Carbon Monoxide Diffusing Capacity in Asthmatic Patients with Mild Airflow Limitation*

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The aim of this study was to test the hypothesis that carbon monoxide diffusing capacity (Dco) is elevated in asthmatic patients with minimal airflow limitation and/or hyperinflation; the latter factors should reduce the possibility of technical errors in the measurement of Dco. In ten asthmatic and ten healthy subjects, Dco and its components, membrane diffusing capacity (Dm) and pulmonary capillary blood volume (Qc) were measured by the single-breath method. Values were normalized for alveolar volume (VA). The mean Dco/VA was higher in the asthma groups as was the Qc/VA. The Dm/Qc was also higher in the asthma group. In the asthmatic but not the healthy subjects, both Dco/VA and Qc/VA were negatively correlated with the forced expiratory flow at 50 percent of vital capacity and peak inspiratory flow rate. Thus, Dco/VA may be increased in asthmatic patients with only mild airflow limitation; this may be due to an elevated capillary blood volume.

Subjects

Ten patients were selected from the Asthma Clinic of the Tygerberg Hospital: all the patients had had documented, recurrent episodes of reversible airway narrowing in response to clearly identified stimuli. All were in a stable condition at the time of investigation and none had chronic sputum production nor evidence of a recent respiratory infection. All the patients were life-long, nonsmokers. The patients were maintained on their usual therapy of inhalational beta-stimulants and beclometasone dipropionate and none had taken oral steroids in the three months prior to the study. Ten healthy, nonsmoking subjects with no history of allergic or respiratory disease or of chronic cough were selected as a reference group. The groups were strictly matched for sex and race and the mean ages were similar (26.5 ± 6.9 vs 27.1 ± 7.3 years; p>0.05).

Informed consent was obtained from all the subjects after the nature of the tests had been fully explained to them.

Methods

Lung mechanics were evaluated in patients and reference subjects from maximal inspiratory and expiratory flow-volume loops and the single-breath nitrogen washout test. The flow-volume curves were recorded from a wedge spirometer (Med Science Corp) and a minimum of three successive loops were obtained from each subject. The expiratory flow-volume curve with the greatest sum of forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) was selected for analysis, as was the inspiratory curve with the greatest peak inspiratory flow (PIFR). The single-breath nitrogen (SN) washout tests were recorded immediately after the flow-volume curves. The washout tests were considered technically acceptable if inspired and expired slow vital capacities were within 5 percent of each other and were within 5 percent of the inspiratory capacity from the best flow-volume curve.

The expired nitrogen concentration was measured with a calibrated, rapid-response nitrogen analyzer (Med Science Corp) and was plotted against expired volume. The expired volume of nitrogen was determined by digital integration of the area under the expired nitrogen-volume curve. The efficiency of alveolar gas mixing was determined by the method of Cumming and Guyatt in which the volume of N₂ recovered is expressed as a percentage of the N₂ volume expected, if gas mixing were perfect.

The single-breath Dco was measured in duplicate at a low oxygen...
(FIO₂ = 0.30) and a high oxygen FIO₂ = 0.80) concentration, at approximately the same time of day in all subjects. A Transfer-test model C apparatus (P. K. Morgan, Ltd) was used and Dco was computed according to the equation given by Clausen.13

The Dco was measured initially at a low oxygen concentration, ensuring that the inspired volume was within ten percent of the inspired vital capacity obtained in the flow-volume loop. Thereafter the patients breathed pure oxygen for five minutes prior to Dco measurements at the high oxygen concentration. In successive measurements, the breathing-hold time was held constant (9 to 11 s) and inspired vital capacity agreed within 5 percent. The rate of reaction of carbon monoxide with hemoglobin (Θ) and the values for the membrane diffusing capacity (Dm) and pulmonary capillary blood volume (Qc) were derived from the formulae given by Cotes.14

In order to normalize Dco values for inter-subject differences in V̇a, the diffusing capacity was also expressed per unit alveolar gas volume (Dco/Va), the latter volume derived by helium dilution during the transfer tests.

Effective breathing-hold time was calculated after Jones and Meade15 and was measured from 3/10 of inspiration to half-way through the alveolar sample. A correction was applied for instrument and anatomic deadspace, the latter taken to be 2.2 ml/kg.16 Washout volume was 900 ml and the alveolar sample was 900 ml. This is similar to the method described by Graham et al17 which was shown to yield results that agreed closely with their three-equation method. Since the hemoglobin concentrations were similar in the two groups, no hemoglobin correction was applied.

Prior to the CO transfer measurements, the hemoglobin (Hb) and carboxyhemoglobin concentrations (HbCO) were measured spectrophotometrically (Instrument Laboratories IL 282), with the CO-oximeter having been calibrated against a commercially available standard specimen prior to the measurements.

In determining differences between the asthmatic and non-asthmatic subjects, both the Student t test and the non-parametric Mann-Whitney U test were used. The two tests yielded similar levels of significance. The values in the tables, and foregoing text, are the mean ± the standard deviation.

**RESULTS**

The group data are summarized in Table 1. The mean FEV₁/FVC of the asthmatic subjects was lower than in the reference group (77.9±10.4 percent vs 89.2± 4.0 percent, p<0.01), as was the maximal mid-expiratory flow; FEF₅₀ (2.4±1.4 vs 4.3±1.0 L/s, p<0.001). Although the slope of phase 3 of the single-breath nitrogen washout curve ∆N₂ was greater in the asthmatic patients (1.6±1.00 vs 0.9±0.5 percent N₂/L, p<0.01), these values are within the range predicted by Buist and Ross17 for normal subjects; gas mixing efficiency18 was also similar in the two groups. The mean closing capacity, expressed as a percentage of total lung capacity (TLC), was, however, greater in the patients (ratio of closing capacity [CC] to TLC 49.4±9.8 percent vs 33.7±4.3 percent, p<0.01). The TLC estimated by the single-breath helium dilution method was lower in the asthmatic group; although the single-breath nitrogen TLC values were also lower in the patients, this difference did not reach statistical significance (Table 1).

The Dco/Va was higher in the asthmatic group (6.3±1.1 vs 5.4±0.4 ml/min/mm Hg/L, p<0.05) as was the Qc/Va (19.3±6.7 vs 12.4±1.7 ml/L, p<0.01) while the ratio Dm/Qc was significantly lower (0.58±0.18 vs 0.89±0.24, p<0.001). The Dco/Va was elevated, i.e., greater than predicted14+1.65 standard errors of the estimate (SEE), in four of the ten patients, but in none of the healthy subjects. In the asthmatic patients, Dco/Va was negatively correlated with both FEF₅₀ and PIFR (p<0.05) (Fig 1).

**DISCUSSION**

The positive findings of this study are that mean Dco/Va and Qc/Va were higher and the Dm/Qc lower in the asthmatic patients when compared with healthy reference subjects; furthermore, Dco/Va and Qc/Va were negatively correlated with both the expiratory (FEF₅₀) and inspiratory (PIFR) indices of airflow.

It has been recognized for many years that the CO diffusing capacity may be normal5,8 or increased5,10 in asthmatic patients and, in this regard, our findings are supportive. More recent studies, however, have concentrated on examining the high/normal Dco values in terms of technical errors in the measurement of Dco that are related in some way to the degree of airflow limitation.5,3,11 It will be argued that the elevated Dco/Va may have a physiologic basis in some patients with mild asthma.

**Table 1—Pulmonary Function in Asthmatic and Reference Groups**

<table>
<thead>
<tr>
<th>Variable*</th>
<th>Asthmatics</th>
<th>Reference</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>26.5±6.9</td>
<td>27.1±7.5</td>
<td>NS</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.61±0.09</td>
<td>1.65±0.09</td>
<td>NS</td>
</tr>
<tr>
<td>TLC (N₂)</td>
<td>4.98±1.34</td>
<td>5.51±1.07</td>
<td>NS</td>
</tr>
<tr>
<td>TLC (He)</td>
<td>4.39±1.28</td>
<td>5.31±0.99</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>RVTLC (N₂) %</td>
<td>31.9±7.8</td>
<td>28.9±5.2</td>
<td>NS</td>
</tr>
<tr>
<td>FVC, liters</td>
<td>3.05±1.14</td>
<td>3.60±0.85</td>
<td>NS</td>
</tr>
<tr>
<td>FEV₁, liters</td>
<td>2.39±0.96</td>
<td>3.28±0.62</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>FEV₁/FVC, %</td>
<td>77.9±10.4</td>
<td>89.2±4.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>FEF₅₀, L/s</td>
<td>2.4±1.4</td>
<td>4.3±1.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>PIFR, L/s</td>
<td>5.3±1.6</td>
<td>5.5±1.2</td>
<td>NS</td>
</tr>
<tr>
<td>∆N₂</td>
<td>1.7±1.0</td>
<td>0.9±0.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Mixing efficiency, %</td>
<td>86.4±5.6</td>
<td>88.1±2.9</td>
<td>NS</td>
</tr>
<tr>
<td>CC/TLC, %</td>
<td>49.4±9.8</td>
<td>33.7±4.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hb, g/dl</td>
<td>13.2±1.1</td>
<td>13.8±0.74</td>
<td>NS</td>
</tr>
<tr>
<td>Dco, ml/min/mm Hg†</td>
<td>26.6±4.6</td>
<td>30.1±6.8</td>
<td>NS</td>
</tr>
<tr>
<td>Dco/Va</td>
<td>6.3±1.1</td>
<td>5.5±0.4</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Qc, ml</td>
<td>79.9±19.2</td>
<td>67.6±13.7</td>
<td>NS</td>
</tr>
<tr>
<td>Qc/Va</td>
<td>19.3±6.7</td>
<td>12.4±1.7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Dm, ml/min/mm Hg</td>
<td>43.8±9.3</td>
<td>59.4±16.4</td>
<td>&lt;0.05</td>
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<tr>
<td>Dm/Va</td>
<td>10.3±1.5</td>
<td>10.7±1.7</td>
<td>NS</td>
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<tr>
<td>Dm/Qc</td>
<td>0.58±0.18</td>
<td>0.89±0.24</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Hb = hemoglobin concentration; FVC = forced vital capacity; FEV₁ = forced expiratory volume in one second; FEF₅₀ = maximal mid-expiratory flow; PIFR = peak inspiratory flow rate; RV = residual volume; TLC = total lung capacity; He = helium; CC = closing capacity; ∆N₂ = slope of phase 3 of the single-breath nitrogen washout; Dco = diffusing capacity of carbon monoxide; Va = TLC in liters; Qc = pulmonary capillary blood volume; Dm = pulmonary membrane carbon dioxide diffusing capacity.

†According to the method of Cumming and Guyatt.16
Gas Mixing

Haydu\(^3\) concluded that the steady-state method of determining DCO gave values which were higher than those obtained from the single-breath method but was unable to demonstrate that DCO was higher in asthma than in health. He attributed the lower single-breath DCO values, relative to the steady-state values, to underestimation of residual volume as a result of poor gas mixing. This contention was confirmed, in part, by Graham et al\(^11\) who demonstrated that the variability of DCO with breath-holding time in conditions of airflow limitation could be correlated with an index of gas mixing, viz, the slope of phase 3 of the single-breath nitrogen washout curve. In the latter study, however, there was no difference after 10 s breath-holding in the DCO between asthmatic and healthy subjects. Although $\Delta N_2$ was higher in the asthmatic group of the present study, both the mean and individual values of the patients and healthy subjects were within the normal range.\(^17\) Furthermore, the gas mixing efficiency of the two groups was similar, as assessed by the Cumming method.\(^15\) It is therefore unlikely that there was significant underestimation of DCO due to poor gas mixing in this study.

Impaired gas diffusion in the terminal airways should be reflected by the membrane diffusing capacity (Dm). Although the Dm was lower in the asthma group, so was the alveolar volume and both DCO and Dm are dependent on the alveolar volume.\(^18\) In view of the evidence presented by Werner and Beneken and Kolmer,\(^19\) all the diffusion values in the present study were normalized by dividing them by the alveolar volume. Consequently, the Dm/VA values in the asthmatic and reference groups were similar. It was not possible to confirm the findings of Pecora et al\(^10\) that Dm or Dm/VA was increased in asthma. This discrepancy may reflect differences in the patients studied, since those authors investigated children with intractable asthma and chronic hyperinflation, whereas there was only mild hyperinflation in the older patients of the present study (ratio of residual volume [RV] to TLC 31.9 ± 7.8 percent vs 28.9 ± 5.2 percent, p>0.05).

Breath-Holding Time

The breath-holding time ($\Delta t$) is a critical variable in the calculation of diffusing capacity.\(^2,11,15,16,19\) Failure to take into account both a portion of the inspiratory time and the expiratory time during alveolar sampling results in underestimation of $\Delta t$ and, therefore, leads to overestimation of DCO. Continuous measurement of both CO and the inert gas (eg, helium) is the ideal and Graham et al\(^10\) have derived an improved, three-equation method of calculating DCO which is more accurate than the conventional, single-equation method.\(^13,14\) However, even in the presence of marked expiratory airflow limitation, the use of $\Delta t$ according to Jones and Meade,\(^15\) and Morris and Crapo\(^16\) appeared to be a satisfactory alternative in the measurement of DCO in asthmatic patients.\(^2\) This was the case, both when the timing of a small alveolar sample (200 ml) was accurately controlled and when a washout volume of 1 L was allowed, prior to taking an alveolar sample of 1 L.\(^2\)

In the study of Graham et al,\(^2\) the overestimation of DCO was slight when using the modified Jones and Meade method (102.7±3.34 percent of the three-equation value) and the degree of overestimation of DCO could be correlated with the degree of expiratory

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**Figure 1.** There was a significant correlation (p<0.01) between the ratio of carbon monoxide diffusing capacity to alveolar volume (DCO/VA) and maximal mid-expiratory flow (FEFM) (a) and between the ratio of pulmonary capillary blood volume (Qc) to VA and FEFMF (b) in the asthmatic subjects.
airflow limitation. Since the modified Jones and Meade method of determining $\Delta t$ and of alveolar sampling were used in the present study, and since the patients had only mild expiratory airflow limitation (FEV₁/FVC 77.9 ± 10.4 percent), it is contended that underestimation of $\Delta t$ was not a significant factor contributing to the higher $D_{CO}/VA$ values in the asthmatic subjects.

**Alveolar Volume**

Another possible explanation for the different values of diffusing capacity values in this study is the significantly lower alveolar volume (TLC$_{va}$) in the asthmatic subjects in whom the helium method resulted in a lower estimate of TLC (by approximately 600 ml or 12 percent) when compared with the single-breath nitrogen method. This may be explained by the fact that in the latter method the mean nitrogen content is determined from the expired vital capacity and not from a small sample of the expired volume. In this respect the difference in the slope of phase 3 of the nitrogen washout between the two groups may indicate a real difference in gas mixing.

By normalizing the $D_{CO}$ and the derived indices for $VA$, one corrects for an underestimation in their values that may result from an underestimation in the alveolar volume.$^{19}$ It is possible, but unlikely, that the asthmatic patients failed to inspire to TLC. This would result in higher values for $Q_c$, as noted by Werner and Beneken Kolmer;$^{15}$ however, the normalization procedure corrects for any such overestimation.$^{15}$ It is therefore likely that, despite differences in alveolar volume, there are real differences in the diffusing capacity and capillary blood volume between the groups. The steady-state method of measuring diffusing capacity would eliminate underestimation of alveolar volume and should, perhaps, be used in future studies of a similar nature.

**Determinants of $D_{CO}/VA$ in Asthma**

There was a clear difference between the two groups with regard to diffusing capacity. Since the hemoglobin concentrations were similar in the two groups and none of the subjects smoked, it is unlikely that discrepancies in the HbCO reaction rate (b) could account for the $D_{CO}/VA$ differences. The remaining possibilities are the membrane diffusing capacity and capillary blood volume.

There was a negative correlation between $D_{CO}/VA$ and indices of expiratory and inspiratory airflow in the asthmatic patients but not in the reference subjects (Fig 2). There was, however, no difference between the mean PIFR in the two groups. The major determinants of PIFR are muscular effort, elastance of the respiratory system and airway resistance. It is unlikely that the static elastic properties of the respiratory system differed very much in the two groups, although this was not measured directly. The presence of lower

**Figure 2.** There was a significant correlation ($p<0.01$) between the ratio of carbon monoxide diffusing capacity to alveolar volume ($D_{CO}/VA$) and peak inspiratory flow rate (PIFR) (a) and between the ratio of pulmonary capillary blood volume and PIFR (b) in the asthmatic patients.

FEV₁, FEV₁/FVC and FEF$_{20}$ values in the asthmatic patients suggests that there was airway narrowing, albeit mild. It is possible that the muscular force necessary to overcome this mildly elevated resistance and to generate normal tidal inspiratory flow rates, also necessitates a more negative mean intra-thoracic pressure. This could possibly account for an increased inflow of blood to the lungs and result in high capillary blood volume values. The correlation between PIFR and FEF$_{20}$ with $Q_c/VA$ are supportive evidence of this hypothesis. Clearly though, direct evidence of differences in pleural pressure is lacking in the present study and must await further definitive investigation. It is therefore probable that a true elevation of the pulmonary capillary blood volume, relative to lung
volume, existed in some of the asthmatic subjects of this study.

CONCLUSION

In a group of asthmatic patients who had only mild expiratory airflow limitation, the pulmonary diffusing capacity per unit alveolar volume was higher than in healthy reference subjects. This is possibly due to an increase in pulmonary capillary blood volume. Steady state diffusion methods would eliminate underestimations of alveolar volume and should probably be used in future studies of this intriguing issue.

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