Single Breath Diffusing Capacity for Carbon Monoxide in Stable Asthma*

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**Background:** Single breath diffusing capacity for carbon monoxide (Dco) is commonly used as a simple method of assessing overall pulmonary gas exchange properties. Studies of Dco in bronchial asthma have yielded conflicting results.

**Objective:** To study Dco and to determine the factors influencing Dco in patients with asthma.

**Methods:** Dco was prospectively measured in 80 consecutive never-smoker patients with uncomplicated stable asthma. The topographic distribution of lung perfusion was determined in 10 asthmatics and 10 controls, with a 133Xe radionuclide scan.

**Results:** The mean (SD) value of Dco was increased to 117 (17) percent of predicted values; individual values were either within or above normal limits; diffusion was also elevated at 116 (19) percent after correction for alveolar volume (transfer coefficient, D/Va). The Dco was not correlated with atopic status, duration of asthma, or results of spirometric tests; there was a weak negative correlation between D/Va and FEV1 or residual volume. There was a better perfusion of the upper zones of the lungs in asymptomatic patients referred to our pulmonary function test (PFT) laboratory for routine preoperative assessment; further inquiry has shown that these patients had bronchial asthma.

Studies of Dco in bronchial asthma have yielded conflicting results; decreased, normal, or increased values have all been reported, both in adults and in children.5

The primary purpose of the present study was to resolve this issue and to establish the fate of Dco among never-smoker, normoglobulin asthmatic patients; as elevated Dco was demonstrated, we attempted to study the factors influencing Dco in asthma, including the topographic distribution of lung perfusion.

**Material and Methods**

Eighty consecutive patients (aged 20 to 68 years; 42 male), who had asthma as defined by American Thoracic Society criteria, were recruited by two of us (P.C., A.F.). To be enrolled in the study, the asthematics had to be normoglobulin and lifelong nonsmokers, because of the well-known negative effect of anemia and smoking on Dco; none of them had arterial hypertension or was using β-blocking agents that can induce asthma. All patients had clinically stable asthma; their treatment consisted of inhaled steroids and bronchodilators for most, with additional oral theophylline for a few. The atopic status was established by clinical history and skin prick testing with a series of common inhalant allergens (Dermatophagoides pteronyssinus, Aspergillus fumigatus, and other common allergens) and with a positive Dco as compared with controls. Among the asthmatics, there was a strong positive correlation between Dco and the apex to base perfusion ratio (r=0.975).

**Conclusions:** Dco is normal or high among never smoker patients with uncomplicated asthma; elevated Dco may be attributed to a better perfusion of the apices of the lungs; the latter could result from two mutually nonexclusive mechanisms: an increase in pulmonary arterial pressure and/or a more negative pleural pressure generated during inspiration as a consequence of bronchial narrowing. The unexpected finding of high Dco should raise the possibility of bronchial asthma in patients with otherwise undiagnosed conditions.

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\[ \text{Dco=} \text{single breath diffusing capacity for carbon monoxide; } \text{DVA=} \text{diffusion per unit of alveolar volume; } \text{PFT=} \text{pulmonary function test; } \text{RV=} \text{residual volume; } \text{Ve=} \text{pulmonary capillary blood volume} \]
Dermatophagoides farinae, pollens, cat fur, dog hair, feathers, and a mixture of molds); total and specific IgE (RAST test) were also determined; 44 of 80 patients were considered atopic. The chest radiographs were unremarkable, except for possible hyperinflation.

Standard techniques were used for measuring PFTs; residual volume (RV) was determined by the 7-min helium dilution technique. Baseline forced expiratory volume in 1 s (FEV1) was 30 to 132 percent of predicted. The single breath diffusing capacity for carbon monoxide was measured in duplicate; it was expressed in absolute value (Dco) and was also calculated per liter of alveolar volume (VA), measured by helium dilution during the 10-s apnea of the Dco maneuver (transfer coefficient, D/VA).

The theoretical values for spirometric data were those from Jouasset. The results of diffusion indices were compared with the predicted values of Frans et al. for male subjects and of Salorinne for female subjects; normal limits for diffusion indices are defined as theoretical ±2 SDs.

Regional lung perfusion was studied in 10 healthy, nonsmoking volunteers and in 10 asthmatics with Dco of 100 to 140 percent of predicted normal, using 133Xe in saline solution as the imaging agent. 133Xe was injected in the left antecubital vein and lung perfusion was determined as previously described, because of the left subclavian artifact, only the right lung was studied; it was divided into 8 equal horizontal slices numbered from 1 (apex) to 8 (bottom).

Measurement of Dco and radionuclide perfusion scan were performed in the seated position. Results are shown as mean ± SD. A one-sample Student's t-test was used to compare actual and theoretical values of Dco and D/VA. A x² test was used to analyze the proportion of asthmatics having more than 100 percent of the theoretical values. Correlation between measurements was assessed using linear regression analysis. A value of p<0.05 was considered to be significant.

RESULTS

Mean (SD) values were 117 (17) percent of predicted for Dco and 116 (19) percent for D/VA, both significantly higher than the normal figures (p<0.05).

Of the 80 asthmatics, 62 had more than 100 percent of the theoretical values for Dco, instead of the expected number of 40 (p<0.01). In 8 of the 80 asthmatics, Dco and D/VA were above and in none below normal limits (Fig 1).

There was no significant correlation between Dco and spirometric data. The linear regression lines between D/VA, and FEV1 or RV, were as follows:

D/VA (percent) = -0.20 FEV1 (percent) +131.15

(r=0.236, p<0.05); D/VA (percent) = -0.12 RV

(percentage) +131.54 (r=0.244, p<0.05).

Atopy and the duration of illness were not correlated with the diffusion indices.

In the group of ten asthmatics in whom a radionuclide scan was performed, the perfusion of the apices was significantly higher than in the ten normal controls (Fig 2). There was a strong positive correlation between Dco (percent of theoretical)
and the apex to base perfusion ratio (uppermost slice compared with lowest slice); \( D_{20} = 0.8528 + 0.82x, r = 0.975, p < 0.001 \) (Fig 3).

**Discussion**

These data indicate that \( D_{20} \) is normal or high among never-smoker patients with uncomplicated asthma.

So far, the mechanisms underlying increased \( D_{20} \) in asthma have remained largely putative. We have previously reported that nitroglycerin diverts pulmonary blood flow to the dependent areas of the lung and causes a decrease in \( D_{20} \),12,13, we hypothesized that a reverse mechanism could be operable in asthma and that the increase in \( D_{20} \) could be related to a better perfusion of the apices.

In order to investigate this hypothesis, we performed a radionuclide lung perfusion scan with \(^{133}\text{Xe} \), a poorly soluble gas; as the blood containing the radioactive tracer flows through the pulmonary capillaries, \(^{133}\text{Xe} \) diffuses into neighboring gas-filled alveoli; hence, regional radioactivity is proportional to capillary blood flow to air-filled alveoli in a given part of the lung, allowing for the establishment of a vertical gradient of blood flow from the bottom to the top of the lung.14

Using this technique, we have shown that in asthma, the increase in \( D_{20} \) is associated with increased perfusion of the upper zones of the lung, thus creating a high regional diffusion-perfusion ratio in relation to total diffusing capacity.

Similarly, Weitzman and Wilson15 have provided evidence that perfusion height is 2 to 4 cm higher in asthmatics than in normal subjects in the upright position; however, no correlation was made between \( D_{20} \) and the height of perfusion.

Better perfusion of the apices could result from two mutually nonexclusive mechanisms: an increase in pulmonary arterial pressure and/or a more negative pleural pressure generated during inspiration as a consequence of bronchial narrowing.

Pulmonary hypertension has been reported in asthma by at least five different authors.16-20

It is known that the pulmonary vasculature is highly reactive and that vasoconstriction can occur as a consequence of hypoxia; others have provided evidence of a significant degree of hypoxic pulmonary vasoconstriction occurring in asthma.21,22 Conceivably, pulmonary vasoconstriction could also be provoked by mediators of airway inflammation, a characteristic feature of asthma.

Keens et al23 have shown that adding external resistance during inspiration causes an increase in \( D_{20} \) in normal subjects. In asthma, inspiration opposes greater resistance due to bronchial narrowing, causing exaggerated negative pleural pressure, so that inflow of blood to the lung and increase in pulmonary capillary blood volume (\( V_c \)) could ensue. Several studies have shown that \( V_c \) is not increased in asthma15,24,25; these measurements, however, were made during quiet breathing and a transient increase in \( V_c \) during breath-hold after rapid maximal inspiration against resistance cannot be ruled out. Measurements of the diffusing capacity of the membrane have yielded conflicting results in asthmatics15,25; partitioning between \( V_c \) and diffusing capacity of the membrane is delicate and has not shed light on the origin of increased \( D_{20} \) in asthma.

The poor correlation between diffusion indices and spirometric abnormalities is in accordance with the poor relationship between gas exchange and indices of airflow obstruction in asthma; it is believed that spirometric indices are mainly determined by bronchoconstriction of large airways, while obstruction of peripheral airways by edema and secretions is more likely to determine ventilation/perfusion imbalance; indeed, there is evidence that reduced expiratory flow and gas exchange impairment are caused by different pathophysiologic mechanisms; also, morphologic studies of bronchial biopsy specimens from asthmatics have demonstrated that conspicuous inflammation may be present even when expiratory flows are normal or only slightly reduced.

In conclusion, we have demonstrated that \( D_{20} \) and \( D/V_A \) are increased in never-smoker asthmatics, irrespective of atopic status or duration of illness; there is a weak negative correlation between \( D/V_A \) and FEV\(_1\) or RV; the relationship between \( D_{20} \) and spirometric indices does not reach the level of statistical significance. The increase in diffusion indices is strongly correlated with a better perfusion of the upper zones of the lung.

This is not only of academic interest; clinical evi-
dence indicates that values of Dco above normal limits are very suggestive of asthma, in the absence of obvious indicators pointing to another cause. Not uncommonly, we have suspected and later confirmed asthma in patients with undiagnosed conditions with increased Dco referred to our PFT laboratory for routine preoperative assessment. Furthermore, Dco is a useful test to better categorize patients suffering from chronic obstructive pulmonary disease, as it is characteristically low in emphysema, normal in chronic bronchitis, and normal or high in uncomplicated asthma; conversely, a decrease in Dco in an asthmatic patient should raise the question of anemia or associated decrease in effective vascular bed (eg, emphysema, interstitial lung disease, pulmonary vascular disease).

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