PULMONARY DIFFUSING CAPACITY IN NORMAL INDIAN SUBJECTS*

By

J.S. GULERIA, M.P. SHARMA, J.N. PANDE AND K. RAMCHANDRAN

Department of Medicine, All-India Institute of Medical Sciences, New Delhi

INTRODUCTION

EVALUATION of pulmonary functions has gained great importance in clinical practice during the last decade. A large number of tests are currently available to assess different functions of the lung whose final aim is to maintain the normal arterial blood gas tensions. The diffusion of respiratory gases across the alveolar-capillary membrane constitutes one of the most important steps in the arterialization of mixed venous blood. The efficiency of this process of diffusion is measured as pulmonary diffusing capacity which has been defined as the quantity of gas in ml. at S.T.P.D. diffusing across the pulmonary membrane per minute per mm Hg. of partial pressure difference between the alveolar air and pulmonary capillary blood (7). Carbon monoxide (CO) is the gas usually employed for the measurement of pulmonary diffusing capacity because its rapid binding with haemoglobin causes little increase in the pulmonary capillary CO tension. The latter can, therefore, be assumed to be zero during a short exposure to the gas in a very low concentration. This obviates the need for complicated integration procedures for the determination of mean pulmonary capillary gas tension. Pulmonary diffusing capacity for carbon monoxide (D_{LCO}) has been shown to be decreased in a variety of lung diseases including pulmonary fibrosis, emphysema, bronchiectasis and interstitial fibrosis. Guleria *et al.* (15, 16) have subdivided patients with chronic obstructive lung disease into two groups on the basis of resting steady state D_{LCO}. Impairment of diffusion was found by Guleria *et al.* (17) to be one of the earliest derangements of pulmonary function in patients with interstitial fibrosis due to scleroderma. The value of D_{LCO} in separating emphysema from chronic bronchitis has been accepted by several investigators (1,12,14,16). In view of its great clinical importance as a test of pulmonary function, it is imperative to establish normal standards for D_{LCO} in order to evaluate the data obtained in pathological states. Normal values of pulmonary diffusing capacity in Indian subjects have not been reported so far. The present study was undertaken, therefore, to standardize the normal values for D_{LCO} in our population.

MATERIALS AND METHODS

One hundred and eighty six normal individuals were included in the study. These volunteers included medical students, doctors, laboratory assistants and healthy relations of the patients attending the medical outpatient department of the A.I.I.M.S. hospital. There were 106 males and 80 females. The details of their age and sex distribution have been given

Received 8-7-1970

in Table I. The age of the subjects was recorded as completed years. Before being included in the study each volunteer had a thorough clinical examination and a straight roentgenogram of the chest to exclude any cardiopulmonary disease. Subjects with hemoglobin concentration <12.0 G% were discarded from the study.

TABLE I

Age and sex distribution of the subjects studied

Age in years	*Males*	*Females*	*Total*
10-14	7	5	12
15-19	10	10	20
20-24	15	9	24
25-29	11	11	22
30-34	10	11	21
35-39	11	10	21
40-44	10	10	20
45-49	13	8	21
50-54	7	3	10
55-59	8	1	9
60-64	4	2	6
10-64	106	80	186

The pulmonary diffusing capacity for carbon monoxide was determined by the modified steady state technique of Bates *et al.* (2) using a Rahn and Otis end-tidal sampling device for obtaining the alveolar air. The infrared CO analyzer and the bag-in-box spirometer sys em were calibrated before starting the study. As carbon monoxide is not commercially available in India, it was prepared in the laboratory by treating formic acid with concentrated sulphuric acid at 100°C. The CO evolved was collected over 5% sodium hydroxide solution to absorb impurities like carbon dioxide. The subjects were made to inhale a mixture containing 0.03-0.04% CO. A steady state was usually achieved after 10-15 breaths when the end-tidal and mixed expired CO concentration became constant. Since carbon dioxide also gives a small deflection in the CO analyzer, a zero correction was estimated by taking the meter readings for end-tidal and mixed expired air before the inhalation of the CO mixture. These readings were subtracted from the final meter reading to obtain the true concentrations of CO in the alveolar and mixed expired air. The DL_{CO} was calculated with the assumption that the mean pulmonary capillary CO concentration remained negligible during the short period of the test. The results were expressed at B.T.P.S. in *ml./min./mm.Hq.*

Standard statistical methods were employed to find out the coefficients of correlation and probability values. Linear regression of DL_{CO} on single independent variables was obtained by the method of least square. For finding out the simultaneous regression with more than one independent variable the covariance matrix method was used (28).

RESULTS

Of the 186 normal individuals studied, 81 males and 55 females were finally included in the statistical analysis of the data. The remaining 25 males and 25 females had to be excluded from the study as they were hyperventilating with minute volumes over 10 L/min. The correlation coefficients and the linear regression of three independent variables, i.e., age, height and body surface area with DL_{CO} in both the sexes have been given in Table II. In the case of females, only the height correlated significantly with DL_{CO}, while in the males all the three independent variables showed significant correlation with DL_{CO}. In view of the absence of any correlation of DL_{CO} with age and body surface area (B.S.A.) in the females, no attempt was made to predict the normal values in them. In the males a multiple regression of DL_{CO} on all the three variables was worked out. However, careful examination of the regression function revealed that after taking the age and height into account, the third variable B.S.A. did not improve the regression function significantly. Hence for the prediction of normal value of DL_{CO} in males, the regression function of DL_{CO} on age and height only was used. The linear regression line of DL_{CO} on both age and height as determined by the covariance matrix method was given by the following expression :

$$DL_{CO} = -8.74 - 0.17 \times \text{Age} + 0.21 \times \text{Height } (cm.)$$

Both the partial regression coefficients in the above equation were statistically significant ($P < 0.05$). An analysis of variance revealed that the regression function gave an adequate fit to the data. The minimum standard error of an individual predicted value was ± 5.2.

TABLE II

The Correlation Coefficients and Regression functions of Age, Height and B.S.A. with DLco

	Males (81)	*Females* (55)
1. Height and DLco		
r	0.22	0.32
P value	<0.05	<0.05
DLco	0.4+0.12 x Ht. (cm)	- 15.7+0.3 x Ht.(cm)
2. Age and DLco		
r	- 0.28	- 0.04
P value	<0.01	NS
DLco	23.8—0.11 x Age	—
3. B.S.A. and DLco		
r	0.22	0.01
P value	<0.05	NS
DLco	—	—

DISCUSSION

The steady state technique for the measurement of pulmonary diffusing capacity suffers from the disadvantage that during hyperventilation the DL_{CO} increases tremendously (22,26,30,31). Some of the subjects in the present series were apprehensive and had a minute volume >10 *L/min.* The calculated DL_{CO} in these hyperventilators was much higher than the values obtained in persons during quiet ventilation. This increase in DL_{CO} may be due to an increase in the pulmonary capillary blood volume producing a large blood-gas interface. Because of obvious reasons, these hyperventilators were not included in calculating the regression equations.

Pulmonary diffusing capacity depends upon a number of factors of which the size of the effective surface area available for gaseous exchange, thickness of the alveolar-capillary membrane, pulmonary capillary blood volume and the haemoglobin concentration are the most important. In normal persons the effective surface area of the pulmonary membrane would be expected to be closely related to functional residual capacity. Since the latter is a function of height and differs in the two sexes, the DL_{CO} also would be likely to be affected by these factors. For the same age and height the females have a lower functional residual capacity (1) and in accordance with this they are also reported to have lower pulmonary diffusing capacity (2,24,70). In the present study the mean DL_{CO} in females was 16.1 *ml/min/mmHg* as compared to the value of 19.9 *ml/min/mmHg* in the males.

A gradual decline in DL_{CO} with advancing age has been reported by McGrath and Thomson (23), Donevan *et al.* (9) and Woolf (31). This observation was confirmed by the present study in male subjects only. In females no significant correlation was found between the age and DL_{CO}. This might probably have been due to the lack of accuracy in the statement of age by the female subjects. It could also be related to a greater apprehension in female subjects during the performance of the test. Moreover, the number of patients over the age of 50 years was rather small.

Cohn *et al.* (6) suggested that the decrease in DL_{CO} with increasing age was probably due to a reduction in pulmonary capillary bed. Bates *et al.* (3) and Cotes *et al.* (8) endorsed their view. Hamer (18) and Solvesteen (29), on the other hand, proposed that the changes in the alveolar membrane were responsible for the reduction of DL_{CO} in older people.

The dependence of DL_{CO} on the body size has been reported by Cohn *et al.* (6), Forster (11) and Lewis *et al.* (20). In conformity with the observations of these investigators, the DL_{CO} was found to vary significantly with height in both the sexes. A significant correlation with B.S.A., however, was observed in male subjects only.

Of the three independent variables, only age and height were required for satisfactory prediction of DL_{CO} in the males. The same parameters have been used by Bates *et al.* (4) for the prediction of DL_{CO} in their subjects. The values of DL_{CO} obtained by the regression equation for the present series of cases are very similar to those predicted by Bates *et al.* (4)

who also utilized the modified steady state technique for the determination of DL_{CO}. Table III shows the normal values of DL_{CO} reported by various investigators all over the world. The data obtained on the present series of volunteers suggest that the pulmonary diffusing capacity in Indians is quite similar to that seen in Western subjects.

TABLE III

Authors	*Method*	*Age in years*	*DLco ml/min/mm Hg*
Krogh (19)	Breath holding	20-50	18-40
Boje (5)	Breath holding	25-60	18-35
Lilienthal *et al.* (21)	Integration procedure	28-36	10-29*
Riley *et al.* (25)	Integration procedure	17-40	14*
Bates *et al.* (2)	Steady state	18-41	11-29
Ogilvie *et al.* (24)	Breath holding	8-72	11-35
Filley *et al.* (10)	Steady state	20-45	13-30
Present study	Steady state	12-64	11-35

*Values converted from DL_{O_2} to DLco by dividing by 1.23

SUMMARY

Regression formulae have been derived for the prediction of pulmonary diffusing capacity as a function of age and height in healthy Indian males. It has been concluded that the pulmonary diffusing capacity in Indian subjects is no different from that seen in the Western people.

REFERENCES

1. Bates, D.V. The measurement of pulmonary diffusing capacity in the presence of lung disease. *J. Clin. Invest.*, **37**: 591, 1958.
2. Bates, D.V., N.G. Boucot and A.E. Dormer. The pulmonary diffusing capacity in normal subjects. *J. Physiol.*, **129**: 237, 1955.
3. Bates, D.V., C.J. Varvis, R.E. Donevan and R.V. Christie. Variations in the pulmonary capillary blood volume and membrane diffusion component in health and disease. *J. Clin Invest.*, **39**: 1401, 1960.
4. Bates, D.V., C.R. Woolf and G.I. Paul. Chronic bronchitis: A report on the first two stages of the co-ordinated study of chronic bronchitis. *Med. Serv. J. Canada*, **18**: 21, 1962.
5. Boje, O. Uber die Grosse der Lungendiffusion des Menschen wahrend Ruhe und Korperliche Arbeit. *Arbeitsphysiol.*, **7**: 157, 1934.

6. Cohn. J.E., D.G. Carroll, B.W. Armstrong, B.H. Shepard and R.L. Riley. Maximal diffusing capacity of lung in normal male subjects of different ages. *J. Appl. Physiol.*, **6**:588, 1954.

7. Comroe, J.H., A. Cournand, J.K.W. Ferguson, G.F. Filley, W.S. Fowler, J.S. Gray, H.F. Helmholtz, Jr., A.B. Otis, J.R. Pappenheimer, H. Rahn and R.L. Riley. Standardization of definitions and symbols in respiratory physiology. *Fed. Proc.*, **9**: 602,1950.

8. Cotes, J.E., D.P. Snidel and B.H. Shepard. Effect of negative intra-alveolar pressure on the pulmonary diffusing capacity. *J. Appl. Physiol.*,**15**:372, 1960.

9. Donevan, R.E., W.H. Palmer, C.P. Varvis and D.V. Bates. Influence of age on pulmonary diffusing capacity. *J. Appl. Physiol.*, **14**:483, 1959.

10. Filley, I.F., D.J. Maclntosh and G.W. Wright. CO uptake and pulmonary diffusing capacity in normal subjects at rest and during exercise. *J. Clin. Invest.*, **33**: 530, 1954.

11. Forster, R.E. Exchange of gases between alveolar air and pulmonary capillary blood: Pulmonary diffusing capacity. *Physiol. Rev.*, **37**:391, 1957.

12. Fraser, R.G. and D.V. Bates. Body section roentgenography in the evaluation and differentiation of chronic hypertrophic emphysema and asthma. *Am. J. Roentgen.*, **82**:39, 1959.

13. Goldman, H.I. and M.R. Becklake. Respiratory function tests. *Amer. Rev. Resp. Dis.*, **79**:457, 1959.

14. Gonzalez, E., H. Weill, M.M. Ziskind and R.B. George. The value of single breath diffusing capacity in separating chronic bronchitis from pulmonary emphysema. *Dis. Chest.*, **53**:229, 1968.

15. Guleria, J.S., R.G. Gupta and J.N. Pande. Chronic obstructive lung disease in Northern India. *Amer. Rev. Resp. Dis.*, **100**:490, 1969.

16. Guleria, J.S. and J.N. Pande. Chronic obstructive lung disease—A review. *Bull. All Ind. Inst. Med. Sci.*, **3**:127, 1969.

17. Guleria, J.S., J.N. Pande, S.K. Malik and L.K. Bhutani. Lungs in progressive systemic sclerosis. *Br. J. Dis. Chest.*, **64**:150, 1970.

18. Hamer, N.A.J. Variation in the components of diffusing capacity as the lung expands. *Clin. Sci.*, **24**:275, 1963.

19. Krogh, M. The diffusion of gases through the lung in man. *J. Physiol.*, **49**:271, 1915.

20. Lewis, B.M., T.H. Lin, F.E. Noe and R. Komisarik. The measurement of pulmonary capillary blood volume and pulmonary membrane diffusing capacity in normal subjects: The effect of exercise and position. *J. Clin. Invest.*, **37**:1061, 1958.

21. Lilienthal, J.L., Jr., R.L. Riley, D.D. Proemmel and R.E. Franke. An experimental analysis in man of the O_2 pressure gradient from alveolar air to arterial blood during rest and exercise at sea level and at altitude. *Am. J. Physiol.*, **147**:199, 1946.

22. MacNamara, J., F.J. Prime and J.D. Sinclair. The increase in diffusing capacity of the lungs on exercise. *Lancet.*, **I**:404, 1960.

23. McGrath, M. and M.L. Thomson. Effect of age, body, size and lung volume change on alveolar-capillary permeability and diffusing capacity in man. *J. Physiol.*, **146**:572, 1959.

24. Ogilvie, C.M., R.E. Forster, W.S. Blakemore and J.W. Morton. A standardized breath holding technique for the clinical measurement of the diffusing capacity of the lung for carbon monoxide. *J. Clin. Invest.*, **36**:1, 1957.

25. Riley, R.L., R.H. Shepard, J.E. Cohn, R.G. Garroll and B.W. Armstrong. Maximal diffusing capacity of lungs. *J. Appl. Physiol.*, **6**:573, 1954.

2.6 Ross, J.C., R. Frayser and J.B. Hickam. A study of the mechanism by which exercise increases the pulmonary diffusing capacity for carbon monoxide. *J. Clin. Invest.*, **38**:916, 1959.

27. Rotman, H.H. and C.R. Woolf. The diffusing capacity of the lungs at rest and on exercise in adults with atrial or ventricular septal defects. *Dis. Chest.*, **43**:613, 1963.

28. Snedecor, G.W. In statistical methods. *5th ed. Iowa States University Press.* pp. 122-142, 1956.

29. Solvesteen, P. Measurement of the lung diffusing capacity for carbon monoxide and of non-uniform ventilation by means of a closed system. *Scand. J. Clin. Lab. Invest.*, **15**:587, 1963.

30. Turino, G.M., M. Brandfonbrener and A.P. Fishman. The effect of change of ventilation and pulmonary blood flow on the diffusing capacity of the lung. *J. Clin. Invest.*, **38**:1186, 1959.

31. Woolf, C.R. An assessment of the fractional carbon monoxide uptake and its relationship to pulmonary diffusing capacity. *Dis. Chest.*, **46**:181, 1964.