Evaluation of diffusing capacity of the lung for carbon monoxide normalized per liter alveolar volume as a parameter for assessment of interstitial lung diseases

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Introduction The single-breath (SB) diffusing capacity for carbon monoxide (DLCO) is the most clinically useful routine pulmonary function test after spirometry and lung volumes. The DLCO is the product of two measurements during breath holding at full inflation: (i) the rate constant for carbon monoxide uptake from alveolar gas and (ii) the accessible alveolar volume (VA). DLCO divided by VA (DLCO/VA), also called Krogh factor, reflects physiology more appropriately. It reflects the diffusing capacity in the available alveolar spaces.

Aim The aim of the study was to assess the validity of DLCO/VA interpretation in patients with interstitial lung diseases.

Patients and methods This study involved 53 patients diagnosed as interstitial lung disease who presented to our pulmonary function laboratory in the Chest Department at Ain Shams University Hospital. Spirometry and DLCO-SB technique were performed.

Results Fifty-three patients with mean age of 47.11 ± 13.7 years were included, 20 women and 33 men. The study showed positive correlation between age and forced vital capacity (FVC) and negative correlation between age and residual volume (RV). Height was significantly statistically related to DLCO, DLCO/VA, and total lung capacity (TLC)-SB. FVC showed no correlation with both DLCO and DLCO/VA. However, it was positively correlated with TLC-SB, VA, RV, and functional residual capacity. The mean of DLCO was 45.62 ± 17.19 and of DLCO/VA was 76.5 ± 31.7. DLCO showed a significant relationship with the following parameters: DLCO/VA, TLC, and RV/TLC. DLCO/VA showed positive statistical correlation with DLCO and TLC and negative correlation with VA. VA was positively correlated with TLC, FVC, and RV. However, it was negatively correlated with DLCO/VA.

Conclusion DLCO and DLCO/VA should be interpreted coherently with each other especially in restrictive lung diseases; in addition, VA and TLC-SB give a good guide for lung volume in interstitial lung disease. *Egypt J Broncho* 2014 8:51–56

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Keywords: alveolar volume, diffusing capacity, DLCO/VA (KCO), forced vital capacity, interstitial lung diseases, spirometry, total lung capacity

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Introduction

The single-breath (SB) test using carbon monoxide (CO) is the most widely used method to measure the pulmonary diffusing capacity. The result is usually expressed for the whole lung [diffusing capacity for carbon monoxide (DLCO)] or per unit alveolar volume (DLCO/VA) [1].

One of the most important clinical indications of DLCO-SB technique is assessing interstitial lung diseases (ILDs), as there is thickening of the alveolar membrane and a diminished total lung capacity (TLC) due to interstitial processes, which may lead to a severe decline in transfer factor. The acinus is disrupted and the diffusion pathway is lengthened. Typical diseases are extrinsic allergic alveolitis, pulmonary vasculitis syndromes, systemic lupus erythematosus, and of course interstitial fibrosis [2].

DLCO/VA represents the diffusing capacity in the available alveolar spaces. In other words, DLCO/VA determines whether the currently available alveolar spaces are functioning normally [3]. In healthy adults, DLCO/VA is ~4–5 ml CO transferred/min/l of lung volume [4].

A normal DLCO/VA cannot exclude ILD. A decreased DLCO/VA, however, strongly suggests parenchymal lung disease (ILD, emphysema) or pulmonary vascular disease (pulmonary hypertension) [3]. In healthy volunteers, DLCO decreases and DLCO/VA increases, if VA is decreased [5].

This study aimed to assess the validity of DLCO/VA interpretation in patients with ILDs.

Patients and methods

Patients

Fifty-three consecutive patients who were referred to undergo spirometry and DLCO-SB in the pulmonary function laboratory of Chest Department, Ain Shams University Hospital and who were diagnosed as ILDs

during the period between May 2011 and May 2012 were recruited. ILDs diagnosis was based on the the clinical history, radiographic abnormalities, low DLCO, and 6-min walk testing; according to an official American Thoracic Society (ATS), the European Respiratory Society (ERS), the Japanese Respiratory Society (JRS), the Latin American Thoracic Association (ALAT) statement, idiopathic pulmonary fibrosis requires evidence-based guidelines for diagnosis and management [6].

Methods

The patients underwent spirometry including forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), FEV1/FVC, and maximal midexpiratory flow (MMEF) (Master Lab; Jaeger, Wurzburg, Germany). The best results were chosen from three efforts following the ATS/ERS guidelines 2005 [7].

They also performed DLCO-SB (Master Lab; Jaeger) with the following technique after determination of ambient conditions by ambient unit and gas analyzer calibration (helium sensor, 2.5–10%; CO sensor, 0.15–0.30%). The patient was asked to approach the mouthpiece and to close his nose with nose-clip. The patient was instructed to breathe quite normally. After at least three breaths, the patient was instructed to exhale as deeply as possible from normal breathing. After maximal expiration, the patient was requested to inhale fast as deeply as possible according to the ATS/ERS recommendations [7]; inspiration was completed within 2–4 s. The patient inhaled a gas mixture of 0.3% CO and a tracer gas helium 10%. The occlusion time automatically starts after 1/3 of inspiration. At the end of inspiration, the patient was prevented from expiration for the period of time set as occlusion time. The patient was asked to keep the mouthpiece in his mouth and hold his breath for 10 s. The pressure curve displayed during the occlusion showed whether the patient had held his breath or whether he had tried to expire or inspire despite the occlusion. After the set occlusion time had expired, the shutter was opened and the patient exhaled smoothly, without hesitation or interruption. Discard volume and sampling volume were exhaled by sampling tube. The gas sample collected for analysis remained in the tube. The remaining air was exhaled by the opened shutter. The sampling valve closed and the patient left the mouthpiece. The measurement program allows the measurement of DLCO and the following additional parameters: Krogh factor (KCO) (DLCO/VA), VA, TLC, residual volume (RV), RV/TLC%, and functional residual capacity (FRC).

Statistical analysis

Analysis of data was performed using statistical program for the social sciences (SPSS, version 20; SPSS Inc., Chicago, Illinois, USA) as follows:

(1) Description of quantitative variables as mean, SD, and range.
(2) Correlation coefficient test was used to rank variables positively or inversely using Pearson's correlation, as all variables are parametric (SD <50% mean).
(3) Regression linear analysis was performed to compare quantitative variables in parametric data (SD <50% mean).

The level of significance was set as:

P value greater than 0.05 was considered a nonsignificant statistical result. *P* value less than 0.05 was considered statistically significant result.

Results

Fifty-three patients with ILD (mean age 47.9 ± 13.7 years) participated in this study. Of these patients, 20 were men and 33 were women, and their BMI was 29.25 ± 7.16.

The mean ± SD spirometric parameters were as follows: FEV1/FVC = 79.19 ± 10.35, FVC = 66.15 ± 15.32, FEV1 = 62.43 ± 14.93, and MMEF = 50.87 ± 24.59. However, the mean ± SD of DLCO-SB parameters were: TLC = 64.81 ± 14.21, VA = 63.2 ± 14.5, DLCO-SB = 45.62 ± 17.19, KCO = 76.51 ± 31.7, RV/TLC = 44.11 ± 10.8, and FRC = 76.56 ± 22.0.

Table 1 shows the descriptive analysis of different parameters revealing that all of them are parametric.

Table 1 Descriptive analysis of different parameters

Parameters	*N*	Minimum	Maximum	Mean	SD
Age	53	19	74	47.92	13.725
HT	53	145	180	163.11	8.322
BMI	53	16	49	29.25	7.160
FEV_1/FVC	53	49	99	79.19	10.350
FEV_1	53	28	98	62.43	14.938
FVC	53	24	102	66.15	15.329
MMEF	53	9	106	50.87	24.591
RV	53	33	201	84.26	33.204
RV/TLC	53	21	79	44.11	10.882
TLC	53	30	102	64.81	14.215
VA	53	27	101	63.21	14.481
DLCO	53	15	77	45.62	17.193
KCO	53	24	205	76.51	31.751
FRC	53	35	140	76.15	22.061
Valid *N*	53				

DLCO, diffusion lung capacity for carbon monoxide; FEV_1, forced expiratory volume in the first second; FRC, functional residual capacity; FVC, forced vital capacity; HT, height; KCO, Krogh factor; MMEF, maximal midexpiratory flow; RV, residual volume; TLC, total lung capacity; VA, alveolar ventilation.

There was statistically significant positive correlation between age and FVC and statistically significant negative correlation between age and RV using Pearson's correlation (Table 2).

Height showed statistically significant positive correlation with both DLCO and FRC using Pearson's correlation (Table 3).

There was statistically significant positive correlation between VA and each of the following parameters, TLC, FVC, RV, and FRC, whereas there was statistically significant negative correlation between VA and KCO using Pearson's correlation (Table 4).

Table 5 shows that the FVC had statistically significantly positive correlation with TLC by SB technique, FRC, and age. There was statistically significant negative correlation between FVC and RV/TLC using Pearson's correlation.

There was no significant correlation between FVC and DLCO-SB, KCO, MMEF, and BMI when statistically tested.

There was statistically significant relationship between FVC and RV using regression linear analysis (Table 6).

There was statistically significant positive correlation between DLCO and KCO using Pearson's correlation (Table 7).

There was statistically significant relationship between DLCO and MMEF, RV/TLC, TLC, and KCO using regression linear analysis. In contrast, there was no significant correlation between DLCO and the following parameters, FVC, RV, FRC, and BMI (Table 8).

Table 2 Correlation of age with forced vital capacity and residual volume

Parameters	FVC	RV
Age		
r	0.369	−0.295
P (significance)	0.007	0.032
N	53	53

FVC, forced vital capacity; RV, residual volume.

Table 3 Correlation of height with diffusion lung capacity for carbon monoxide and functional residual capacity

Parameters	DLCO	FRC
Height		
r	0.332	0.283
P (significance)	0.015	0.040
N	53	53

DLCO, diffusion lung capacity for carbon monoxide; FRC, functional residual capacity; FVC, forced vital capacity; RV, residual volume.

Table 4 Correlation between alveolar volume and other different pulmonary function parameters

Parameters	FVC	TLC	RV	FRC	KCO
VA					
r	0.607	0.992	0.738	0.807	−0.339
P (significance)	0.000	0.000	0.000	0.000	0.013
N	53	53	53	53	53

FRC, functional residual capacity; FVC, forced vital capacity; KCO, Krogh factor; RV, residual volume; TLC, total lung capacity; VA, alveolar ventilation.

Table 5 Correlation of forced vital capacity with other different pulmonary function parameters and age

Parameters	TLC	RV/TLC	FRC	Age
FVC				
r	0.616	−0.397	0.343	0.369
P (significance)	0.000	0.003	0.013	0.007
N	53	53	53	53

FRC, functional residual capacity; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity.

Table 6 Relationship between FVC as a dependent variable and all of the following predictors: height, BMI, MMEF, RV, RV/TLC, TLC, VA, DLCO, KCO, and FRC

Models	Coefficients[a]			*t*	Significance
	Unstandardized coefficients				
	B	SE	Standardized coefficients (β)		
Constant	6.144	35.466		0.173	0.863
HT	0.027	0.175	0.015	0.157	0.876
BMI	−0.249	0.218	−0.116	−1.142	0.260
MMEF	0.031	0.052	0.050	0.600	0.552
RV	−0.415	0.078	−0.899	-5.343	0.000
RV/TLC	−0.129	0.175	−0.092	−0.736	0.466
TLC	1.381	0.794	1.280	1.739	0.089
VA	0.114	0.725	0.108	0.157	0.876
DLCO	−0.065	0.267	−0.073	−0.245	0.808
KCO	0.098	0.149	0.202	0.656	0.516
FRC	0.009	0.104	0.014	0.091	0.928

DLCO, diffusion lung capacity for carbon monoxide; FRC, functional residual capacity; FVC, forced vital capacity; HT, height; KCO, Krogh factor; MMEF, maximal midexpiratory flow; RV, residual volume; TLC, total lung capacity; VA, alveolar ventilation; [a]Dependent variable: FVC.

Table 7 Correlation between diffusion lung capacity for carbon monoxide and Krogh factor

Parameters	DLCO	KCO
DLCO		
r	1	0.781**
P (significance)		0.000
N	53	53
KCO		
r	0.781**	1
P (significance)	0.000	
N	53	53

DLCO, diffusion lung capacity for carbon monoxide; KCO, Krogh factor; **Correlation is significant at the 0.01 level (two-tailed).

The results showed that KCO had statistically significant positive correlation with DLCO and statistically significant negative correlation with TLC using Pearson's correlation (Table 9).

There was statistically significant relationship between KCO and DLCO, MMEF, RV/TLC, and TLC using regression linear analysis Table 10.

Table 8 Relationship between DLCO as a dependent variable and all of the following predictors: FVC, BMI, MMEF, RV, RV/TLC, TLC, and KCO

Models	Coefficients[a]			*t*	Significance
	Unstandardized coefficients		Standardized coefficients (β)		
	B	SE			
Constant	−21.337	6.610		−3.228	0.002
FVC	−0.010	0.094	−0.0008	−0.102	0.919
BMI	−0.157	0.103	−0.066	−1.525	0.135
MMEF	−0.083	0.028	−0.119	−2.922	0.006
RV	0.006	0.059	0.011	0.097	0.923
RV/TLC	−0.306	0.092	−0.193	−3.313	0.002
TLC	0.837	0.174	0.658	4.803	0.000
KCO	0.552	0.022	1.022	25.035	0.000
FRC	−0.091	0.055	−0.118	−1.652	0.106

DLCO, diffusion lung capacity for carbon monoxide; FRC, functional residual capacity; FVC, forced vital capacity; KCO, Krogh factor; MMEF, maximal midexpiratory flow; RV, residual volume; TLC, total lung capacity; [a]Dependent variable: DLCO.

Table 9 Correlation of Krogh factor with diffusion lung capacity for carbon monoxide and total lung capacity

Parameters	DLCO	TLC
KCO		
r	0.781	−0.345
P (significance)	0.000	0.011
N	53	53

DLCO, diffusion lung capacity for carbon monoxide; KCO, Krogh factor; TLC, total lung capacity.

Table 10 Relationship between KCO as a dependant variable and all of the following predictors: DLCO, FVC, BMI, MMEF, RV, RV/TLC, TLC, and FRC

Models	Coefficients[a]			*t*	Significance
	Unstandardized coefficients		Standardized coefficients (β)		
	B	SE			
Constant	42.469	11.182		3.798	0.000
DLCO	1.697	0.068	0.915	25.035	0.000
FVC	0.092	0.165	0.043	0.560	0.578
BMI	0.293	0.180	0.066	1.625	0.111
MMEF	0.145	0.050	0.113	2.936	0.005
RV	0.031	0.104	0.033	0.299	0.766
RV/TLC	0.535	0.162	0.182	3.297	0.002
TLC	−1.616	0.288	0.685	-5.617	0.000
FRC	0.171	0.097	0.119	1.766	0.084

DLCO, diffusion lung capacity for carbon monoxide; FRC, functional residual capacity; FVC, forced vital capacity; KCO, Krogh factor; MMEF, maximal midexpiratory flow; RV, residual volume; TLC, total lung capacity; [a]Dependent variable: KCO.

Discussion

Reduction in VA by disease processes is the largest potential source of error in interpreting DLCO. Correction for the effect of altered VA has been attempted by reporting the ratio of DLCO/VA [8]. DLCO/VA was introduced in clinical practice mainly to allow for reductions in VA brought about by a loss of pulmonary tissue, as for example, following pneumonectomy [9]. Englert [10] showed, in 74 patients, that pneumonectomy resulted in a reduction of TLC to 58% of predicted, with DLCO and DLCO/VA being 70 and 114% of predicted, respectively. It is clear that, in such instances, a correction for DLCO by the participant's VA is warranted, as the decrease in DLCO following pneumonectomy is of a totally different nature than that caused by a thickened alveolar capillary membrane, as in lung fibrosis, or by lung destruction, as in emphysema. However, such simple correction for DLCO by VA may not be appropriate in all circumstances [9].

Ayers *et al.* [9] considered interstitial fibrosis to be an example of loss of lung units, leading to the maintenance of a normal DLCO/VA ratio.

Cotes *et al.* [11] stated that the predictions for DLCO depend on age, sex, and height. VA depends on sex and height but not on age. In adults, KCO depends inversely on age and height but, in a review of the literature, hardly at all on sex [12].

In this study, we did not find any statistical relationship or correlation between DLCO, DLCO/VA, and age or sex; however, height showed statistically significant positive correlation with DLCO.

Stam *et al.* [13] stated that DLCO increases and DLCO/VA decreases exponentially with height. As TLC is also exponentially related to height, both DLCO and DLCO/VA are linearly related to TLC.

The variability between our results and the other studies may be related to the limited number of patients in our studies, and they based their statements on healthy population.

In this study, there was a statistically significant positive correlation between FVC and TLC-SB, RV/TLC, and FRC, but there was no correlation of FVC with DLCO and DLCO/VA. These are in agreement with several researchers results [9,14], which show no statistical relationship between DLCO, DLCO/VA, and the parameters of spirometry.

Agusti *et al.* [2] and Frans *et al.* [15] observed that, in patients with a restrictive pattern of pulmonary function, DLCO/VA is proportionally less decreased

than DLCO. Their results are in acceptance with our results, as the mean of DLCO/VA and DLCO was 76.51 and 45.62, respectively. In addition, they reported that the opposite trend has been observed in patients with an abnormally high VA.

Although our study reported a statistically significant positive correlation between DLCO and KCO, a study on 2313 patients showed large differences and much variability between the two parameters [16].

However, such variability between our study and Johnson's study related to different subgroups in his study; there were patients with asthma, emphysema, extrapulmonary lung disease, ILD, and lung resection in his study, whereas our study was on a single group with ILD. In addition, our study was on a limited number of patients compared with his study; Johnson [16] also stated that, as VA decreased, DLCO decreased linearly and KCO increased.

In searching for the validity of the DLCO test as providing an assessment of lung volume, a study [16] was conducted comparing VA with TLC determined by plethysmography. The VA provides the lung volume in which helium is distributed during the DLCO test. The ILD group had low lung volumes, but their VA was near their TLC (VA 91 ± 17% of TLC), which was not the case in groups of moderate-to-severe obstruction where TLC was increased and the VA was lower than TLC, being 58 ± 15% of TLC. In our study, the mean of TLC and VA was 64.8 ± 14.21 and 63.2 ± 14.5, respectively; VA represents 97.5% of TLC. One of the advantages of the DLCO-SB occurs at TLC level, which is a reproducible reference point. It was reported [17] that VA lays within 10% of TLC and as the difference is related to the anatomic dead space and the gas mixing in 10 s breath hold is incomplete, it can be concluded that the VA and TLC-SB can be a good guide for lung volume in patients with ILD.

It is worth to mention the relationship between DLCO and lung volume; however, it is not linear and markedly less than 1 : 1. Hence, these simple ratios as traditionally reported do not provide an appropriate way to normalize DLCO for lung volume [18].

In criticizing the DLCO/VA, Forster [19] mentioned that the changes in DLCO with lung volume in patients with mixed airway and alveolar disease are complex, which can make it potentially misleading to use DLCO/VA as an index. Hughes and Pride [20] noted that DLCO/VA does not correct either for failure to reach maximal lung volume or for pathologically reduced lung volumes.

We have to point that DLCO and DLCO/VA are usually compared with predicted values, which are determined in healthy volunteers, who by definition have a normal TLC. Thus, the current predicted values relate to measurements made at normal TLC [11]. In patients with a restrictive ventilatory defect (i.e. a reduced TLC) or with a larger than normal TLC, a comparison with predicted values at predicted TLC can lead to erroneous conclusions. A decrease in lung volume will cause a decrease in surface area, and consequently in DLCO. However, DLCO/VA is higher at reduced VAs compared with predicted values estimated at a normal TLC [17]. Stam *et al*. [12] suggested that, in restrictive pulmonary disease, DLCO and DLCO/VA should be compared with predicted values at a lung volume equal to the patients actual TLC. Therefore, they derived reference values for DLCO/VA as a function of VA. Their results were corroborated by Chinn *et al*. [18] and Frans *et al*. [15], who found a comparable relationship between DLCO and VA. However, a disadvantage of such a method is that both predicted values of DLCO and DLCO/VA at predicted TLC and the volume correction procedure have their own variability [17].

Hughes and Pride [20] stated that KCO enhances understanding of DLCO. It is clear that the nonlinear relationship between KCO and lung volume precludes DLCO/VA from being a volume correction for the DLCO when VA is reduced, but KCO remains a true reflection of alveolar CO uptake efficiency at a given volume. They mentioned that the emphasis on DLCO/VA as a correction factor for lung volume is misconceived and reflects a misapprehension of the physiology. Hence, they believe the term DLCO/VA should be replaced by the more informative term, KCO.

Our findings must be considered in the context of the limitations of this study. First, we did not correct the DLCO values for hemoglobin concentration, as this information was not available in all patients. This certainly may have changed the DLCO and DLCO/VA values; however, it should have changed both equally, and thus not affected the primary purpose of our study, which was to compare the two values. Second, we accounted on TLC-SB technique rather than TLC measured by body plethysmography, which is more accurate, because it was not requested by the patients physicians to limit the costs. However, the TLC-SB and VA at low lung volumes give reproducible results we can account on.

Conclusion

In interpretation of DLCO-SB, the DLCO/VA ratio should not be neglected and should be in coherence with the interpretation of DLCO, as decreased DLCO/VA strongly suggests parenchymal lung disease. However, alone it does not provide a valid index of the effect of changes in VA; it may lead to errors in interpretation of the diffusing capacity. VA and TLC-SB could be good indicators of lung volume in patients with ILD, which need further investigations on a wide scale.

Acknowledgement

Conflicts of interest

None declared.

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