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Different K_{CO} and V_A combinations exist for the same DL_{CO} value in patients with diffuse parenchymal lung diseases

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Abstract

Background: DL_{CO} is the product of the CO transfer coefficient (K_{CO}) by the "accessible" alveolar volume (V_A). In theory, the same DL_{CO} may result from various combinations of K_{CO} and V_A values, each of which reflect different injury sites and mechanisms. We sought to determine in this study the potential variability of both V_A and K_{CO} for fixed values of DL_{CO} in diffuse parenchymal lung diseases (DPLD).

Methods: To this end, we designed a retrospective, cross-sectional study of three distinct types of DPLD and analysed pulmonary function test (PFT) datasets.

Results: We show here that for the same value of DL_{CO} (50 % predicted), K_{CO} varied from 60 to 95 % predicted and V_A from 55 to 85 % predicted in various types of DPLD idiopathic pulmonary fibrosis, sarcoidosis and connective tissue disease-associated DPLD, indicating distinct pathogenic mechanisms in these diseases. In addition, a comparison of V_A with total lung capacity may help to evidence the distal airway obstruction sometimes associated with certain DPLD particularly sarcoidosis.

Conclusion: Clinicians should take into account not only DL_{CO} but also V_A and K_{CO} values when managing patients with DPLD.

Keywords: Carbon monoxide diffusing capacity, DL_{CO}, Carbon monoxide transfer coefficient, K_{CO}, Interstitial lung disease

Background

The single-breath carbon monoxide diffusing capacity (DL_{CO}) is the product of two measurements during breath holding at full inflation: the rate constant for carbon monoxide uptake from alveolar gas (K_{CO} [$minute^{-1}$]) and the "accessible" alveolar volume (V_A). Consequently, the same DL_{CO} may result from various combinations of K_{CO} and V_A values. Changes in each of K_{CO} and V_A may reflect different injury sites and mechanisms. In theory, the decrease in DL_{CO} may result from a fall in V_A (mainly due to restrictive and/or obstructive defects) and/or a fall in K_{CO} (due to alveolar/capillary damage or a microvascular disease). Few studies have focused on the significance of DL_{CO} in diffuse parenchymal lung diseases (DPLD) [1–5], highlighting the prognostic value of its component K_{CO}. No study to our knowledge has sought to assess the validity of the above mentioned theory in the context of DPLD. Our primary objective in the present study was to assess in a large cohort of distinct types of DPLD the potential variability of both V_A and K_{CO} for fixed values of DL_{CO}. A secondary objective was to determine whether a low V_A value in this context might reflect a distal airway obstruction in addition to a potential restrictive defect. To this end, we designed a retrospective, cross-sectional study of three distinct types of DPLD: idiopathic pulmonary fibrosis (IPF, the prototype for fibrotic pulmonary diseases predominantly affecting the lower lobes), stage IV sarcoidosis (predominantly affecting the upper lobes) and connective tissue disease-associated interstitial lung

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diseases (CTD-ILDs, which are usually characterized by diffuse, inflammatory lesions rather than fibrotic damage).

Methods

Each of three university hospitals in France provided pulmonary function test (PFT) datasets from around 80 DPLD patients (75, 80 and 87 patients, respectively). Pulmonary function tests had been performed according to international recommendations and had used similar quality criteria [6–8]. Only raw PFT data were provided and % predicted values were subsequently calculated by a single investigator (CD2) for the whole population according to Stanojevic for spirometry [9] and other international recommendations for DL_{CO} and static lung volumes respectively [10, 11]. The PFTs (spirometry, body plethysmography and single-breath carbon monoxide transfer) using routine techniques had been performed for clinical purposes. We got approval from the Institutional Review Board of the French learned society for respiratory medicine – Société de Pneumologie de Langue française, which judged our study as fully observational and which therefore did not require any informed consent.

Two-hundred and forty-two patients with complete datasets were retrospectively assigned to IPF (n = 85), sarcoidosis (n = 73) or CTD-ILD (n = 84) groups. Patients with IPF and CTD-ILD exhibited lower values of DL_{CO} than those with sarcoidosis (43 ± 18 % predicted (11-89 %), 44 ± 15 (12-88 %), and 56 ± 18 % (19-115 %), in IPF, CTD-ILD and sarcoidosis, respectively, $p < 0.0001$). Then, three PFT datasets (one per group) were matched for DL_{CO} % predicted (agreement 5 %, by a single investigator (CD2)) to allow comparisons of the groups at similar levels of DL_{CO}. Consequently, 77 patients were excluded from the analysis due to matching selection (for instance

Table 1 Demographic and functional characteristics of the study participants

	IPF n = 55 gr. 1	Sarcoidosis n = 55 gr. 2	CTD-ILD n = 55 gr. 3	P value (ANOVA)	Between-groups difference
Centre 1/2/3, n	15/22/18	12/25/18	29/12/14	0.007	Not tested
Gender, F/M	15/40	27/28	24/31	0.048	Not tested
Age, years	71 ± 8	52 ± 11	60 ± 14	<0.001	2<3<1
Height, cm	167 ± 9	168 ± 10	167 ± 9	0.812	
History of smoking (never/ex/current smokers)	23/27/5	33/19/3	25/26/4	0.383	
FEV_1, L	2.17 ± 0.69	1.87 ± 0.65	2.18 ± 0.66	0.023	Not tested
FEV_1, % predicted	82 ± 21	59 ± 17	74 ± 15	<0.001	2<3<1
FVC, L	2.65 ± 0.68	2.66 ± 0.81	2.65 ± 0.89	0.994	
FVC, % predicted	74 ± 19	66 ± 15	68 ± 15	0.053	
FEV_1/FVC	0.83 ± 0.07	0.71 ± 0.14	0.84 ± 0.07	<0.001	Not tested
FEV_1/FVC, % predicted	109 ± 10	90 ± 17	108 ± 9	<0.001	2<1-3
TLC, L	4.50 ± 1.23	4.67 ± 1.20	4.39 ± 1.15	0.486	
TLC, % predicted	75 ± 16	80 ± 17	75 ± 15	0.147	
FRC, L	2.51 ± 0.69	2.65 ± 0.64	2.53 ± 0.70	0.582	
FRC, % predicted	77 ± 18	87 ± 25	81 ± 20	0.038	1<2
RV, L	1.76 ± 0.47	1.90 ± 0.69	1.67 ± 0.41	0.078	
RV, % predicted	73 ± 18	97 ± 30	80 ± 22	<0.001	1-3<2
RV/TLC	0.40 ± 0.06	0.41 ± 0.09	0.39 ± 0.07	0.362	
V_A, L	3.66 ± 0.96	3.70 ± 0.92	3.66 ± 1.01	0.972	
K_{CO}, mmol/min/kPa/L	1.00 ± 0.23	1.20 ± 0.30	1.07 ± 0.30	<0.001	
K_{CO}, % predicted	75 ± 17	77 ± 20	72 ± 19	0.507	Not tested
DL_{CO}, mmol/min/kPa	3.68 ± 1.37	4.45 ± 1.65	4.02 ± 1.66	0.040	
DL_{CO}, % predicted	**48 ± 15**	**49 ± 14**	**47 ± 16**	**0.737**	Not tested
V_A/TLC	0.81 ± 0.06	0.80 ± 0.08	0.83 ± 0.06	0.047	3>2

Abbreviations: *IPF* idiopathic pulmonary fibrosis, *CTD-ILDs* connective tissue disease-associated interstitial lung diseases, *FVC* forced vital capacity, FEV_1 forced expiratory volume in 1 s, *FRC* forced respiratory capacity, *TLC* total lung capacity, DL_{CO} carbon monoxide diffusing capacity, K_{CO} rate for carbon monoxide uptake, V_A alveolar volume

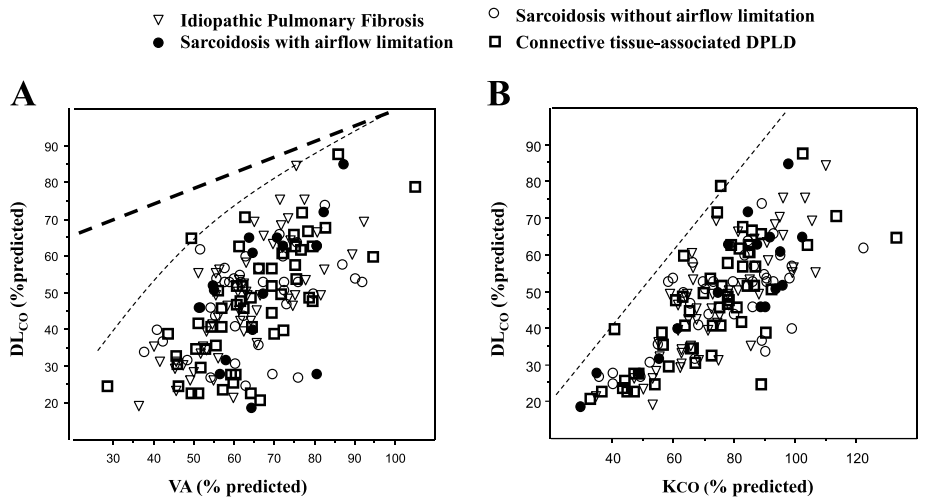

Fig. 1 Relationships between DL_{CO} on one hand and V_A (left panel) and K_{CO} (right panel) on the other. Circles represent sarcoidosis (closed: with airflow limitation, n = 17; open: without airflow limitation). **a** Dotted lines describe "reduced expansion" (upper bold line) and "loss of units" effects, calculated according to Hughes and Pride [4]. Patients with DPLD lied in the discrete to diffuse loss of alveolar unit areas. **b** The dotted line is the identity line for the DL_{CO}-K_{CO} plot; patients along this line have normal V_A and the reduced DL_{CO} is related to a decrease in K_{CO} due to microvascular pathology

IPF and CTD-ILD subjects with very low DL_{CO} % predicted values and sarcoidosis subjects with high DL_{CO} values). Results were expressed as means ± SD. Continuous variables were compared using the Student's *t*-test or the analysis of variance (ANOVA, see Table) as appropriate. The chi-squared test was used for the comparison of qualitative variables (smoking history). Statistical significance was defined by a p value <0.05. All analyses were performed using the Statview 4 package (SAS institute, Grenoble, France).

Results

One hundred and sixty-five PFT datasets (55 per group) were analysed (Table 1). The three study groups had similar mean values for K_{CO} and V_A as well as for DL_{CO} (the matching criterion). However, on an individual patient basis, a similar DL_{CO} could be obtained from various combinations of K_{CO} and V_A (Fig. 1). This figure clearly shows that K_{CO} can vary from decreased (diffuse loss of units) to normal or barely increased (discrete loss of units) values. We show here that for a similar DL_{CO} value of 50 % predicted, for instance, K_{CO} varied from 60 to 95 % predicted and V_A from 55 to 85 % predicted.

In addition, 17 patients exhibited an airflow limitation (FEV_1/FVC < lower limit of normal). They all belonged to the sarcoidosis group (Table 1). The reduction in alveolar volume (measured using a dilution technique) relative to total lung volume (TLC, measured using body plethysmography), expressed as V_A/TLC, was correlated with parameters of central airway obstruction (FEV_1/FVC: $r^2 = 0.10$, $p < 0.001$) and even more strongly with distal airway obstruction (RV/TLC: $r^2 = 0.25$, $p < 0.001$). Since the V_A/TLC value of the population as a whole may seem lower than expected (Table 1) even in patients without significant airflow limitation (n = 148, FEV_1/FVC = 0.82 ± 0.06), we further evaluated whether some patients exhibited a small airways obstructive syndrome defined by a normal FEV_1/FVC ratio and a greater reduction of both FEV_1 and FVC than TLC (FVC % predicted/TLC % predicted < 0.80). We found 20 such subjects, described in Table 2. Similarly to proximal airflow limitation,

Table 2 Small airway obstructive syndrome (SAOS) in patients without proximal airflow limitation (FEV1/FVC > lower limit of normal)

Characteristic	With SAOS	Without SAOS	P value
	N = 20	N = 128	
IPF/sarcoidosis/CTD-ILD, n	2/11/7	53/27/48	0.002
Gender, F/M	14/6	45/83	0.006
Age, years	54 ± 14	64 ± 13	0.003
Body mass index, $kg.m^{-2}$	25.8 ± 5.3	26.2 ± 3.8	0.664
FEV_1, % predicted	55 ± 13	78 ± 17	<0.001
FVC, % predicted	54 ± 14	72 ± 16	<0.001
FEV_1/FVC, % predicted	101 ± 13	107 ± 10	0.031
TLC, % predicted	75 ± 17	76 ± 15	0.786
FRC, % predicted	83 ± 23	78 ± 19	0.309
RV, % predicted	98 ± 27	76 ± 19	<0.001
RV/TLC	0.48 ± 0.07	0.38 ± 0.06	<0.001
V_A/TLC	0.77 ± 0.07	0.83 ± 0.05	<0.001

Abbreviations: *IPF* idiopathic pulmonary fibrosis, *CTD-ILDs* connective tissue disease-associated interstitial lung diseases, *FVC* forced vital capacity, FEV_1 forced expiratory volume in 1 s, *FRC* forced respiratory capacity, *TLC* total lung capacity, V_A alveolar volume

small airways obstructive syndrome was predominantly present in sarcoidosis.

Discussion

Our present study confirms that an abnormally low DL_{CO} can result from very different combinations of the primary measurements K_{CO} and V_A. This was the case for all three types of DPLD. Furthermore, the assessment of V_A/TLC [12], the latter being obtained from body plethysmography, may suggest both central or peripheral airway obstruction and this was observed particularly in sarcoidosis thereby providing additional clues to the pathogenic features of this condition. We recently described diseases associated with a small airway obstructive syndrome (a non-specific pattern frequently observed in pulmonary function testing units [13]). It is noteworthy that in that study, sarcoidosis and interstitial pneumonia were two of the conditions associated with this pattern. In the present work, we extend our previous data showing that a DPLD can exhibit a mixed pattern associating both a restrictive syndrome and a small airways obstructive syndrome.

Conclusions

In conclusion, we confirmed that the components of DL_{CO} (K_{CO} and V_A) may largely vary in DPLD while DL_{CO} appears constant. The magnitudes of K_{CO} and V_A values might indicate distinct disease mechanisms and thereby bear a relative prognostic value in addition to giving clues to pathogenesis of these diseases. For these reasons, clinicians should take into account not only DL_{CO} but also V_A and K_{CO} when seeking to assess DPLD, in order to provide a more informed and better care to these patients.

Abbreviations

DL_{CO}: carbon monoxide diffusing capacity; K_{CO}: rate for carbon monoxide uptake; V_A: alveolar volume; DPLD: diffuse parenchymal lung disease; IPF: idiopathic pulmonary fibrosis; CTD-ILDs: connective tissue disease-associated interstitial lung diseases; PFT: pulmonary function test; SDS: standard deviation score; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 second; FRC: forced respiratory capacity; TLC: total lung capacity; sRaw: specific airway resistance.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

JP, DIB and CD2 designed the cohort design and analysis plan. Analyses were performed by CD2. All authors (JP, LP, CP, RB, HN, CD2 and DIB) contributed to recruitment, data collection, discussion of results and final approval of the submitted manuscript.

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