Evaluation of carbon monoxide diffusing capacity as an early detection of pulmonary involvement in rheumatoid arthritis patients without respiratory symptoms

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Background The risk of death for rheumatoid arthritis (RA) patients with interstitial lung disease (ILD) is three times higher than that in RA patients free from ILD.
Therefore, this study was carried out to assess the value of carbon monoxide diffusing capacity (DL_{CO}) in the early detection of pulmonary involvement in RA.

Patients and methods This prospective study was carried out in 30 nonsmoker patients with RA (29 women and one men) ranging in age from 21 to 66 years, mean age 42.6 ± 1.9 years. All RA patients were clinically free from respiratory symptoms with normal chest radiograph. For all patients, spirometry and DL_{CO} were performed.

Results Twenty (66.67%) cases had a diffusion defect in DL_{CO}; the defect was mild in 17 cases and moderate in three cases. The severity of DL_{CO} differed significantly with the duration of RA and decrease in forced vital capacity ($P < 0.05$), but did not differ significantly with either the rheumatoid factor titer or the duration of methotrexate therapy ($P > 0.05$), although the use of methotrexate was higher among patients with abnormal DL_{CO}. The severity of DL_{CO} correlated significantly and inversely with the duration of RA ($P < 0.05$). A normal pattern of spirometry was the predominant pattern, followed by a restrictive pattern and small airway obstruction, whereas the obstructive pattern was the least observed.

Conclusion There is a high incidence of pulmonary involvement in RA patients, especially in those receiving methotrexate therapy. Pulmonary function testing, and more specifically DL_{CO}, can serve as useful screening tools for the early detection of RA-ILD even in clinically asymptomatic patients with normal chest radiograph.
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Keywords: carbon monoxide diffusing capacity, interstitial lung disease, methotrexate, rheumatoid arthritis

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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by infiltration of the synovium with inflammatory cells. More aggressive forms of RA involve extra-articular tissues, causing lung inflammation, splenomegaly with cytopenia, skin nodules, and vasculitis [1].

Interstitial lung disease (ILD) is an increasingly recognized complication of RA that contributed toward significantly increased morbidity and mortality. The diagnosis can be challenging as patients are unlikely to report dyspnea because of an overall decrease in physical activity with advanced arthritic symptoms [2].

In view of the above, this study was carried out to assess the value of carbon monoxide diffusing capacity (DL_{CO}) in the early detection of pulmonary involvement in respiratory symptom-free nonsmoker patients with RA whose chest radiograph was normal.

Patients and methods

This prospective study included 30 patients with RA recruited from the outpatient clinic of the Rheumatology Department of Ain Shams University Hospital. RA was diagnosed according to the 2010 American College of Rheumatology and European League Against Rheumatism classification criteria [3]. For all patients, the following were documented: detailed medical history, thorough clinical examination, plain chest radiograph, full laboratory investigations including rheumatoid titer, full spirometric study, and DL_{CO}. The following patients were excluded from the study: patients with concurrent lung disease, patients with occupational history predisposing to lung disorder, patients who cannot undergo perform pulmonary function tests (PFTs) and DL_{CO}, patients with clinical or laboratory evidence of other collagen vascular disease, smokers, patients with abnormal chest radiograph, and cardiac patients. All patients provided consent to participate and the study was approved by the institutional ethical committee.

Lung function

Forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC), FEV_1/FVC ratio, and forced expiratory flow over 25–75% part of FVC ($FEF_{25–75\%}$) were measured using the spirometry

system (Masterscreen 2001, version 4.5; Erich Jaeger GmbH, Friedberg, Germany). Readings were performed in triplicate, with the highest values recorded and expressed as a percentage of the predicted value according to the guidelines of the American Thoracic Society (ATS) [4].

Categorization of abnormal functional patterns with respect to PFTs was performed according to the guidelines of the ATS [4] as follows:

(1) Large airways obstructive pattern if the FEV_1/FVC ratio was less than 0.7.
(2) Small airways obstructive pattern if the $FEF_{25–75\%}$ value was reduced with a normal FEV_1/FVC ratio without a restrictive pattern.
(3) Restrictive pattern if the predictive percent of FVC less than 80%, provided that the FEV_1/FVC ratio was normal.

Carbon monoxide diffusing capacity single-breath method

DL_{CO} was measured using the system (Masterscreen 2001, version 4.5; Erich Jaeger GmbH) according to the ATS guidelines [5]. The following activities were avoided before the carbon monoxide diffusing capacity single-breath (DL_{CO} sb) method study according to the guidelines of the ATS [5] as follows:

(1) Vigorous exercise within 30 min of testing.
(2) Consumption of a large meal within 2 h of testing.
(3) Inhalation of supplemental oxygen for 10 min before the test.

The procedure for the DL_{CO} sb method was as follows:

(1) The equipment was calibrated with a 3-l syringe.
(2) The tests were explained to the patients.
(3) The patient was asked about the activities that should be avoided before the tests.
(4) The weight was recorded to the nearest kilogram and height was measured to the nearest centimeter without shoes.
(5) The patient was in a sitting position with the head slightly elevated.
(6) The mouthpiece was placed in the mouth and the patients were instructed to close their lips around the mouthpiece.
(7) Tidal breathing had to be carried out for a sufficient time to ensure that the patient was comfortable with the mouthpiece.
(8) Deep inspirations had to be avoided during this period as they could increase subsequent CO uptake.
(9) The DL_{CO} maneuver began with unforced exhalation to residual volume.
(10) At residual volume, the patient's mouthpiece was connected to a source of test gas and the patient inhaled rapidly to total lung capacity (TLC).
(11) The patient was asked to hold his/her hold breath by maintaining full inspiration using only the minimal effort necessary. The breath-hold time was for about 10 s.
(12) Then, the patient exhaled maximally.

Acceptable test criteria for DL_{CO} are as follows:

(1) Use of proper quality-controlled equipment.
(2) Inspired volume of 85% of largest vital capacity in 4 s.
(3) A stable calculated breath hold for 10 s. There should be no evidence of leaks, or Valsalva or Mueller maneuvers.
(4) Expiration in 4 s with appropriate clearance of dead space (VD) and proper sampling/analysis of alveolar gas.

The extent of severity of DL_{CO} sb was evaluated according to the ATS guidelines [5] as follows:

(1) Normal: 80–120% of predicted.
(2) Mild: less than 80% but more than 60% of predicted.
(3) Moderate: less than 60% but more than 40% of predicted.
(4) Severe: less than 40% of predicted.

Statistical analysis

Parametric numerical data were expressed as mean ± SD, whereas nonparametric numerical data were expressed as number and percentage. A χ^2-test was used to compare two qualitative variables. One-way analysis of variance was used to compare more than two groups in terms of quantitative variables. Spearman's correlation test was used to rank different variables against each other positively or inversely. Linear regression analysis was used to determine the relationship between dependent and independent variables. Statistical significance was set at *P* value less than 0.05. Statistical analyses were carried out utilizing statistical package for the social sciences (SPSS) software (version 12.0; SPSS Inc., Chicago, Illinois, USA) for Windows.

Results

Thirty patients with RA were included in this study. The basic characteristics of all the patients included are shown in Table 1.

On comparing spirometric affection and DL_{CO} severity, among the 10 patients with normal DL_{CO}, seven had normal spirometry, one had an obstructive

pattern, one had a restrictive pattern, and one had small airway disease. Among the 17 patients with a mild diffusion defect, 10 had normal spirometry, two had an obstructive pattern, three had a restrictive pattern, and two had small airway disease. Among the three patients with a moderate diffusion defect, two had normal spirometry and one had small airway affection. The comparison was statistically nonsignificant ($P > 0.05$) (Table 2).

When the comparison was performed between the mean values of FEV_1 and the severity of DL_{CO}, the difference was not statistically significant ($P > 0.05$) (Table 3). Comparison with the mean values of FVC was statistically significant ($P < 0.05$) (Table 4), whereas comparison with FEV_1/FVC was not statistically significant ($P > 0.05$) (Table 5).

Comparison between methotrexate therapy intake and the severity of DL_{CO} showed that in patients with normal DL_{CO} 2/10 patients received methotrexate, in patients with a mild defect, 14/17 patients received methotrexate, whereas in patients with a moderate defect, 3/3 patients received methotrexate. The comparison between methotrexate intake and the severity of DL_{CO} was statistically significant ($P < 0.05$) (Table 6). When the mean duration of methotrexate therapy (in months) was compared with the severity of DL_{CO}, the result was statistically nonsignificant ($P > 0.05$) (Table 7).

The duration of RA (in months) was compared with the severity of DL_{CO}; the result of comparison was statistically significant ($P < 0.05$) (Table 8). Moreover, comparison between rheumatoid factor level and the severity of DL_{CO} was statistically nonsignificant ($P > 0.05$) (Table 9). Logistic regression showed that

Table 1 Basic characteristics of the patients included

Variables	Value
Age (years)	42.6 ± 1.9
Sex (male/female) [*N* (%)]	1/29 (3.33/96.67)
Rheumatoid factor [*N* (%)]	
Negative	6 (20)
Positive	24 (80)
DL_{CO} sb [*N* (%)]	
Normal	10 (33.3)
Mild	17 (56.67)
Moderate	3 (10)
DL_{CO} sb (% predicted)	
Normal	84.4 ± 3.12
Mild	67.9 ± 4.78
Moderate	57.6 ± 0.70
Spirometry [*N* (%)]	
Normal	19 (63.33)
Obstructive	3 (10)
Restrictive	4 (13.33)
Small airway disease	4 (13.33)
Methotrexate [*N* (%)]	
No	11 (36.67)
Yes	19 (63.33)

DL_{CO} sb, carbon monoxide diffusing capacity single-breath.

Table 2 Comparison between spirometry and the severity of carbon monoxide diffusing capacity

Spirometry	DL_{CO} [*N* (%)]			
	Normal	Mild	Moderate	Total
Normal	7 (23.3)	10 (33.3)	2 (6.6)	19 (63.3)
Obstructive	1 (3.3)	2 (6.6)	0	3 (10)
Restrictive	1 (3.3)	3 (10)	0	4 (13.3)
Small airway	1 (3.3)	2 (6.6)	1 (3.3)	4 (13.3)
χ^2	2.642			
P	0.852			

DL_{CO}, carbon monoxide diffusing capacity.

Table 3 Comparison between forced expiratory volume in the first second and severity of carbon monoxide diffusing capacity

DL_{CO}	FEV_1		ANOVA	
	Range	Mean ± SD	*F*	*P*
Normal	83.5–119.2	94.250 ± 9.555	2.946	0.070
Mild	58–118	82.282 ± 14.305		
Moderate	79–92	84.667 ± 6.658		

ANOVA, analysis of variance; DL_{CO}, carbon monoxide diffusing capacity; FEV_1, forced expiratory volume in the first second.

Table 4 Comparison between forced vital capacity and severity of carbon monoxide diffusing capacity

DL_{CO}	FVC		ANOVA	
	Range	Mean ± SD	*F*	*P*
Normal	77–126	102.390 ± 13.515	3.379	0.049
Mild	49.6–119.9	87.600 ± 15.658		
Moderate	88–92	90.467 ± 2.157		

ANOVA, analysis of variance; DL_{CO}, carbon monoxide diffusing capacity; FVC, forced vital capacity.

Table 5 Comparison between forced expiratory volume in the first second/forced vital capacity and severity of carbon monoxide diffusing capacity

DL_{CO}	FEV_1/FVC		ANOVA	
	Range	Mean ± SD	*F*	*P*
Normal	70.7–93	79.249 ± 7.449	0.112	0.894
Mild	58.98–99	81.062 ± 11.193		
Moderate	75–83	80.000 ± 4.359		

ANOVA, analysis of variance; DL_{CO}, carbon monoxide diffusing capacity; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity.

Table 6 Comparison between methotrexate and severity of carbon monoxide diffusing capacity

Methotrexate therapy	DL_{CO} [*N* (%)]			
	Normal	Mild	Moderate	Total
No	8 (26.67)	3 (10)	0 (0)	11 (36.67)
Yes	2 (6.67)	14 (46.67)	3 (10)	19 (63.33)
χ^2	13.577			
P	0.001			

DL_{CO}, carbon monoxide diffusing capacity.

the severity of DL_{CO} correlated significantly and inversely with the duration of RA ($P < 0.05$) (Fig. 1).

Discussion

ILD is a common extra-articular manifestation of RA [6], with a three-fold higher risk for mortality in RA patients with ILD in comparison with those without ILD [7]. Owing to these facts, this study was carried out in an attempt to evaluate the value of DL_{CO} in the early detection of pulmonary involvement in respiratory symptom-free nonsmoker patients with RA whose chest radiograph was normal, especially considering that the prevalence of asymptomatic preclinical ILD among individuals with RA is unknown [8]. In this study, the transfer factor for carbon monoxide (TLCO) is widely used in pulmonary function laboratories because it represents a unique non-invasive window on pulmonary microcirculation [9].

In the current study, women outnumbered men in accordance to other studies [10,11] reporting that women are more often commonly affected by RA than men. The abnormal diffusion defect in DL_{CO} was observed in 20 (66.67%) patients, being mild in 17 (56.67%) cases and moderate in three (10%) cases, whereas the remaining 10 (33.33%) patients had normal DL_{CO}. These findings were in agreement with those of several studies; Sakai *et al.* [12] reported decreased DL_{CO} in 45.5% of the RA patients, Gabazza *et al.* [13] reported decreased DL_{CO} in 56% of RA patients, and Provenzano [14], in his study, showed that transfer factor of the lung for carbon monoxide (TLCO) was less than 75% in 50% of the RA patients. However, Chen *et al.* [6] found that DL_{CO} was reduced in 47 (45%) patients. One previous study [15] reported a relatively lower incidence for decreased DL_{CO}, being only 23%; this small percentage could be attributed to the disease duration of the patients, which was less than 2 years, suggesting a relatively short duration for pulmonary affection to occur.

A normal spirometric pattern was the predominant pattern (63%) in this study, followed by a restrictive pattern and small airway obstruction, whereas the obstructive pattern was observed the least. These findings were in agreement with those of several studies [14,16]. Kanat *et al.* [17] found that in asymptomatic RA patients, the normal pattern in PFTs was the predominant pattern, followed by a large airways obstructive pattern with small airways disease; their results may be attributed to the fact that they did not exclude smokers. In our study, all the patients selected were lifelong nonsmokers and therefore the obstructive pattern was the least observed.

The comparison between the severity of DL_{CO} and FVC in our study was statistically significant. Moreover, the more severe the diffusion defect, the more severe the restriction in the lung FVC. This result was in agreement with the study of Gabbay *et al.* [15], who found that decreased FVC in the absence of airflow obstruction was present in patients and was always associated with abnormal DL_{CO}.

Table 7 Comparison between duration of methotrexate and severity of carbon monoxide diffusing capacity

DL_{CO}	Duration of methotrexate therapy		ANOVA	
	Range	Mean ± SD	*F*	*P*
Normal	4–84	44.000 ± 56.569	0.482	0.628
Mild	2–84	23.500 ± 24.329		
Moderate	24–30	27.000 ± 4.243		

ANOVA, analysis of variance; DL_{CO}, carbon monoxide diffusing capacity.

Table 8 Comparison between duration of rheumatoid arthritis and severity of carbon monoxide diffusing capacity

DL_{CO}	Duration of RA		ANOVA	
	Range	Mean ± SD	*F*	*P*
Normal	2–96	40.200 ± 29.642	20.834	<0.05
Mild	2–120	47.588 ± 32.663		
Moderate	120–240	180.000 ± 60.000		

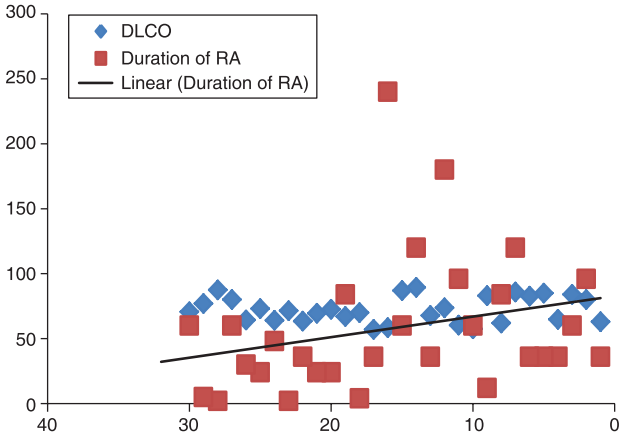
ANOVA, analysis of variance; DL_{CO}, carbon monoxide diffusing capacity; RA, rheumatoid arthritis.

Table 9 Comparison between rheumatoid factor levels and severity of carbon monoxide diffusing capacity

DL_{CO}	Rheumatoid factor levels (IU/dl)		ANOVA	
	Range	Mean ± SD	*F*	*P*
Normal	18–320	110.857 ± 123.601	0.155	<0.857
Mild	32–256	89.643 ± 71.641		
Moderate	45–170	108.333 ± 62.517		

ANOVA, analysis of variance; DL_{CO}, carbon monoxide diffusing capacity.

Fig. 1



Linear regression analysis between the severity of carbon monoxide diffusing capacity (DL_{CO}) and the duration of rheumatoid arthritis (RA).

In the current study, a significant correlation was observed between the duration of RA (in months) and the severity of DL_{CO}. This finding was in agreement with that of Chen *et al*. [6] who reported that RA-ILD patients had longer disease duration. Similarly, Yin *et al*. [18] found that disease duration may be considered a risk factor for RA-ILD. Yet, the rheumatoid factor levels did not correlate significantly with the severity of DL_{CO} in our study as reported previously in other studies [6,18].

The incidence of RA patients receiving methotrexate therapy in our study was higher among patients with abnormal DL_{CO} and the correlation between the use of methotrexate therapy and the severity of DL_{CO} affection was statistically significant, even though on further analysis there was no significant correlation between duration of methotrexate use and the severity of DL_{CO}. This result was partially in agreement with that of Gochuico *et al*. [8] who assessed progressive preclinical ILD in 64 RA patients in Maryland (USA) using high-resolution computed tomography and PFTs; they found that patients with progressive preclinical RA-ILD had statistically significant higher frequencies of treatment using methotrexate than those with stable RA-ILD and concluded that methotrexate use is a cause of progression of RA-ILD. Conversely, this result was not in agreement with that of Gabbay *et al*. [15], who found that although in their study, the period of use of methotrexate was short, yet, the use of methotrexate in the management of RA did not differ across the groups and was not associated with DL_{CO} levels. They reported that, in accordance to previous work, in the absence of acute pneumonitis, use of methotrexate is not associated with the development of restrictive physiology or deterioration in gas exchange. Dawson *et al*. [19] have reported an interesting study on the chronic pulmonary effects of methotrexate in patients with RA. In their prospective study, which incorporated high-resolution computed tomography assessment and serial PFTs, there was no evidence of association of methotrexate with chronic pulmonary fibrosis. Interestingly, even in the subgroup of RA patients with evidence of pulmonary fibrosis at the beginning of the study, methotrexate did not cause any deterioration in pulmonary function over a 2-year period. Moreover, Yin *et al*. [18] also found that treatment with methotrexate or other chemicals was not significantly associated with RA-ILD.

In conclusion, there is a high incidence of pulmonary involvement in RA patients, especially in those receiving methotrexate therapy. DL_{CO} represents an effective, noninvasive technique for the detection of RA-ILD, even in the absence of clinical symptoms, making this procedure an effective screening tool for early ILD that may allow institution of more aggressive therapy directed toward the prevention of end-stage, fibrotic lung disease.

Finally, it is recommended to screen for pulmonary involvement in RA patients, even clinically asymptomatic patients, using regular and routine PFTs including DL_{CO}, especially in those with prolonged disease duration and receiving methotrexate therapy.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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