

# Lung clearance of $^{99m}\text{Tc}$ -DTPA in systemic lupus erythematosus

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## Abstract

The early demonstration of lung involvement in systemic lupus erythematosus (SLE) patients is a difficult but important task. In the present study we attempted to identify abnormalities in pulmonary clearance of  $^{99m}\text{Tc}$ -DTPA in SLE, correlating their clearance data with clinical findings and disease activity. Forty-six consecutive SLE patients with and without active disease (LACC score) and 30 normal volunteers were studied. All subjects were submitted to pulmonary scintigraphy with  $^{99m}\text{Tc}$ -DTPA to evaluate the pulmonary clearance, and to a chest X-ray, and SLE patients were submitted to tests of disease activity, spirometry, arterial blood gases and tests to assess acute-phase proteins. Pulmonary clearance was faster in SLE patients with active disease when compared to normal controls [half-life of 67.04 min (51.52-82.55 min) in active SLE versus 85.87 min (78.85-92.87 min) in controls,  $P < 0.05$ ] and there was a higher frequency of abnormal clearance rates in patients with active disease (11 of 26 patients, 42.3%) when compared with SLE patients without disease activity (2 of 20 patients, 10%) ( $P = 0.04$ ). A significant correlation was observed between the clearance rates and cough ( $P < 0.05$ ), but not between the clearance rates and dyspnea symptoms or radiological findings, duration of SLE disease, antinuclear antibody titers and patterns, C-reactive protein or anti-double stranded DNA antibodies. We conclude that the pulmonary clearance of  $^{99m}\text{Tc}$ -DTPA is increased in SLE patients with active disease.

## Key words

- Pulmonary epithelial permeability
- Lung clearance
- Technetium-99m-labeled diethylenetriamine pentaacetic acid
- Systemic lupus erythematosus

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## Introduction

The clearance rate of inhaled technetium-99m-labeled diethylenetriamine pentaacetic acid ( $^{99m}\text{Tc}$ -DTPA) from the alveolar space to the blood provides an index of pulmonary epithelial permeability (1), which has been used to detect early disease in collagen vascular diseases (2-4). These studies demonstrate that lung permeability is frequently

abnormal in patients with systemic sclerosis even when a chest X-ray and lung function tests are normal (3). When the high resolution chest CT is normal, abnormalities of  $^{99m}\text{Tc}$ -DTPA clearance may indicate lung disease at a still earlier stage.

Pulmonary involvement in patients with systemic lupus erythematosus (SLE) has been assessed by clinical findings, chest X-ray, high resolution chest CT, pulmonary func-

tion tests, bronchoalveolar lavage, and lung biopsy (5). The purpose of the present study was to investigate abnormalities in pulmonary clearance of  $^{99m}\text{Tc}$ -DTPA in SLE and correlate them with clinical findings, pulmonary function tests, chest X-ray, disease activity, acute-phase proteins and anti-double stranded DNA antibodies.

## Material and Methods

### Study population and design

SLE patients were selected consecutively from the rheumatology in- and outpatient clinics of a general university hospital during a period of approximately 18 months. Patients were eligible to enter the study if they a) fulfilled the 1982 revised criteria of the American Rheumatism Association for SLE (6), b) were older than 18 years, and c) were nonsmokers or former smokers who had quit at least 30 days before inclusion in the study. Patients were excluded from the study if they a) were known or suspected to be pregnant or nursing, b) had significant medical problems and were unable to perform the diagnostic tests proposed by the study, and c) had connective tissue diseases other than SLE.

The lupus activity criterion count (LACC) (7) was used to assess disease activity. A score of 2 or more constitutes active disease (group III). Group II included SLE patients without active disease.

A control group of healthy volunteers (hospital employees) was used to define normal values for the  $^{99m}\text{Tc}$ -DTPA clearance rate. The volunteers were nonsmokers or former smokers who had quit at least 30 days before inclusion in the study. They were older than 18 years, had no known disease, no respiratory symptoms at least 1 month prior to the study, their chest X-rays were normal, and their screening questionnaire for SLE (8) had less than three items answered affirmatively.

All patients were submitted to pulmonary scintigraphy with a radioaerosol of  $^{99m}\text{Tc}$ -DTPA, a chest X-ray and clinical and laboratory tests for the determination of disease activity, spirometry, arterial blood gases and other laboratory tests to assess acute-phase proteins and isolated indices of SLE activity, all within 36 h of inclusion in the study.

The study was approved by both the Radiation Safety Committee and Ethics and Research Committee of Hospital de Clínicas de Porto Alegre, and all subjects gave informed written consent before their inclusion.

### Determination of the pulmonary clearance rate of $^{99m}\text{Tc}$ -DTPA

$^{99m}\text{Tc}$  was eluted from a  $^{99m}\text{Tc}$  generator (IPEN-TEC  $^{99m}\text{Tc}$  Generator, Instituto de Pesquisas Energéticas e Nucleares, São Paulo, SP, Brazil) and diluted in saline. Twenty millicurie of sodium pertechnetate was introduced into a vial containing DTPA (DTPATEC-S, Sorin Biomedica S.p.A., Saluggia, Italy) to produce  $^{99m}\text{Tc}$ -DTPA and reconstituted with normal saline to a 5-ml volume. The aerosol of  $^{99m}\text{Tc}$ -DTPA was generated by a commercially available nebulizer at a flow of 9 l/min of oxygen (Aerogama<sup>®</sup>, Medical, Porto Alegre, RS, Brazil). This system has been characterized as producing a particle with a mass median aerodynamic diameter of 0.86  $\mu\text{m}$  and a geometric standard deviation of 0.89. The subjects inhaled the aerosol for 3 min at their normal tidal volume while seated. Radioactivity was measured immediately after the inhalation in the prone position and continuous counts were made over the chest and recorded every 20 s for 30 min using an Anger-type scintillation gamma camera (Gamma Müvek MB 9200, Budapest, Hungary). Two regions of interest were created by defining a rectangle as close as possible around each lung field activity with the contours determined auto-

matically. The clearance rate was expressed as the half-time ( $T_{1/2}$ ), i.e., the time for the activity to decrease to 50% of the peak value. For each subject, the  $T_{1/2}$  was determined for both the left and right lung.

### Clinical findings and pulmonary function tests

Demographic data and medical history were obtained and physical examination was performed at the time of inclusion. The presence of respiratory symptoms (dyspnea and cough), duration of SLE disease and the current drug treatment were recorded.

Pulmonary function measurements included spirometry and arterial blood gases. A posteroanterior and lateral chest X-ray was obtained for each volunteer on the same day as the determination of pulmonary clearance of  $^{99m}\text{Tc}$ -DTPA. The chest X-rays were assessed by the same experienced radiologist who was unaware of the clinical, laboratory or pulmonary function status of the patients.

Other laboratory tests carried out to assess acute-phase proteins and isolated indices of SLE activity included: erythrocyte sedimentation rate (Wintrobe),  $\alpha_1$ -globulin,  $\alpha_2$ -globulin,  $\beta$ -globulin and  $\gamma$ -globulin (electrophoresis in agarose),  $\alpha_1$ -acid glycoprotein and C-reactive protein (turbidimetric measurement; Behring Turbitimer, Marburg, Germany), complement component C3 (nephelometry; Behring BNII), antinuclear antibodies (ANA, indirect immunofluorescence), and anti-double stranded DNA (*Crithidia luciliae* assay).

### Statistical analysis

Quantitative nonparametric variables for the three groups studied were compared by the Kruskal-Wallis test. Comparisons between the two groups of SLE patients were made by the Mann-Whitney U-test. Correlations were assessed using Spearman's rank

correlation. Quantitative parametric variables were compared by one-way analysis of variance, followed by the LSD test, and by the unpaired Student *t*-test. Qualitative data were analyzed by the chi-square test with Yates' correction if necessary or by Fisher's exact probability test. The normal range for  $^{99m}\text{Tc}$ -DTPA clearance was defined in the normal volunteers (values lying within two standard deviations of the mean value). On this basis, a clearance half-time of less than 48 min was regarded as abnormal. The level of statistical significance was set at  $P < 0.05$ .

### Results

Seventy-six subjects were included in the study. Thirty were normal volunteers (group I) and 46 were SLE patients divided into group II, inactive SLE (20 patients), and group III, active SLE (26 patients) according to LACC score. Patient characteristics are summarized in Table 1. The groups differed significantly in sex, age, weight, height and smoking history. No correlation was observed between the values obtained for clearance rates and those obtained for sex, age, weight, and height and, for ex-smokers, pack-year index and time of smoking interruption.

Rates of  $^{99m}\text{Tc}$ -DTPA clearance ( $T_{1/2}$  in min) are shown in Table 2.  $T_{1/2}$  values for left lung, right lung and average of both lungs

Table 1. Characteristics of subjects.

	Group I (Control) (N = 30)	Group II (Inactive SLE) (N = 20)	Group III (Active SLE) (N = 26)	P*
Male/female	15/15	1/19	5/21	0.001
Age (years)	30.5 ± 5.8	40.6 ± 11.3	33.0 ± 10.3	<0.001
Weight (kg)	68.6 ± 11.4	62.7 ± 10.7	58.6 ± 13.9	0.01
Height (cm)	170.3 ± 9.4	158.0 ± 6.9	158.7 ± 8.4	<0.001
Smoking history				
Ex-smokers (%)	3 (10%)	7 (35%)	12 (46%)	0.009

Age, weight and height are reported as means ± SD. \*Chi-square test for sex and smoking history, Kruskal-Wallis test for age and one-way analysis of variance for weight and height. SLE, systemic lupus erythematosus.

were significantly lower in group III (active SLE) than in group I (control;  $P < 0.05$ , LSD test). Clearance was abnormal (values lower than 48 min) in 12 (26.09%) of 46 SLE

patients for the left lung, in 13 (28.26%) for the right lung, and in 13 (28.26%) for the average of both lungs. The percentage of clearance abnormalities was also greater in group III (active disease) than in group II (inactive disease).

Associations of the clearance rates and clinical data (Tables 3, 4 and 5) included: a) statistical association between the clearance rates for left lung, right lung and average of both lungs and the cough symptom ( $P < 0.05$ ), but not between the clearance rates and dyspnea symptom or radiological findings, b) no significant correlation between the clearance rates and the duration of SLE disease ( $P > 0.05$ ), c) poor correlation between clearance rates and  $PCO_2$  values ( $r = 0.35$ ,  $P = 0.02$ ), and d) no correlation with ANA titer ( $P > 0.05$ , Spearman's correlation), patterns of ANA, C-reactive protein or anti-double stranded DNA.

## Discussion

The results of this study showed that the pulmonary clearance of  $^{99m}Tc$ -DTPA was faster (shorter half-life) in SLE patients with active disease when compared with normal controls. Although differences in age, sex distribution, weight, height and smoking history between patients and controls were observed, these variables did not appear to influence lung clearance rates and we do not believe that they could explain the faster clearance in active SLE patients. Also there was a higher frequency of abnormal clearance rates in SLE patients with disease activity when compared with SLE patients without disease activity. These findings probably reflect the injury to the pulmonary epithelium induced by the immunological activity of SLE disease.

The main concern in the study design was the difficulty to obtain an adequate "gold standard" for diagnosing SLE pulmonary disease. The diagnosis of primary pulmonary involvement in SLE depends on the

Table 2. Pulmonary clearance rates of  $^{99m}Tc$ -DTPA ( $T_{1/2}$ ) in systemic lupus erythematosus (SLE) patients.

	Group I (Control) (N = 30)	Group II (Inactive SLE) (N = 20)	Group III (Active SLE) (N = 26)	P*
Left lung ( $T_{1/2}$ , min)	86.63 (79.52-93.74)	85.55 (70.62-100.48)	68.24 (52.58-83.89)	0.006
Right lung ( $T_{1/2}$ , min)	83.87 (76.38-91.36)	83.37 (70.09-96.65)	65.84 (49.98-81.69)	0.01
Average of both lungs ( $T_{1/2}$ , min)	85.87 (78.85-92.87)	84.46 (71.02-97.89)	67.04 (51.52-82.55)	0.005

Data are reported as means (95% confidence interval). \*Kruskal-Wallis test; LSD test provided P values lower than 0.05 for comparisons between groups I and III.

Table 3. Spearman's correlation (r) between clearance rates of  $^{99m}Tc$ -DTPA ( $T_{1/2}$ ) and age, weight, and height in SLE patients and, for ex-smokers, pack-year index and time of smoking interruption.

	Left lung clearance (r/P)	Right lung clearance (r/P)	Average clearance (r/P)
Age	0.03/0.81	0.04/0.77	0.03/0.78
Weight	0.02/0.87	0.04/0.76	0.03/0.80
Height	0.11/0.34	0.06/0.63	0.09/0.45
Pack-year index	-0.29/0.19	-0.30/0.17	-0.31/0.17
Smoking interruption (months)	0.14/0.53	0.17/0.44	0.17/0.44

Table 4. Spearman's correlation (r) between clearance rates of  $^{99m}Tc$ -DTPA ( $T_{1/2}$ ) and pulmonary function tests in SLE patients.

	Left lung clearance (r/P)	Right lung clearance (r/P)	Average clearance (r/P)
FVC	0.06/0.72	0.13/0.41	0.11/0.48
FEV <sub>1</sub>	0.02/0.90	0.09/0.57	0.07/0.67
FEV <sub>1</sub> /FVC	0.05/0.74	0.03/0.82	0.04/0.80
FEF <sub>25-75%</sub>	0.09/0.57	0.16/0.30	0.14/0.37
PaO <sub>2</sub>	-0.21/0.19	-0.26/0.09	-0.24/0.12
PaCO <sub>2</sub>	0.37/0.01*	0.32/0.04*	0.35/0.02*
AaPO <sub>2</sub>	0.009/0.95	0.07/0.67	0.05/0.77

FVC = forced vital capacity, FEV<sub>1</sub> = forced expiratory volume in 1 s, FEF<sub>25-75%</sub> = forced expiratory flow at 25-75% of maximal lung volume, PaO<sub>2</sub> = arterial O<sub>2</sub> pressure, PaCO<sub>2</sub> = arterial CO<sub>2</sub> pressure, AaPO<sub>2</sub> = alveolo-arterial gradient of PO<sub>2</sub>.

\*Significant correlation at  $P < 0.05$ .

exclusion of secondary causes capable of inducing parenchymatous lung changes, such as infections and adverse reactions to drugs (5). This exclusion diagnosis requires fiberoptic bronchoscopy with bronchoalveolar lavage, bronchial brushing with a protected catheter and/or transbronchial lung biopsies to be performed routinely in all SLE patients, a procedure that was not ethically acceptable in asymptomatic patients. Therefore, the diagnostic value and the clinical utility of <sup>99m</sup>Tc-DTPA clearance rates in the diagnosis of early pulmonary involvement in SLE will require studies with a prospective design, probably including evaluation of the diffusing capacity of carbon monoxide, which was not possible in the present study. Such study is currently underway. However, the observations in systemic sclerosis (2-4), as well as one prior experience with SLE (9), suggest the potential usefulness of diffusion measurements for SLE patients. In this last study, Lin et al. (9) found that 3 of 7 asymptomatic SLE patients with abnormal <sup>99m</sup>Tc-DTPA clearance had abnormal chest X-ray findings.

In the present study there was a significant relationship between the clearance rates and the cough symptom, but not between the clearance rates and dyspnea symptom. A plausible explanation for these findings might be that in SLE patients dyspnea is related not only to parenchymatous pulmonary involve-

Table 5. Spearman's correlation (r) between clearance rates of <sup>99m</sup>Tc-DTPA (T<sub>1/2</sub>) and acute-phase proteins and isolated indices of SLE activity.

	Left lung clearance (r/P)	Right lung clearance (r/P)	Average clearance (r/P)
C3	0.06/0.68	0.02/0.89	0.04/0.81
C4	0.09/0.57	0.02/0.92	0.05/0.72
CH <sub>100</sub>	0.34/0.03*	0.27/0.08	0.33/0.04*
α <sub>1</sub> -Acid glycoprotein	-0.13/0.41	-0.18/0.26	-0.16/0.31
α <sub>1</sub> -Globulin	-0.03/0.84	0.10/0.52	0.04/0.81
α <sub>2</sub> -Globulin	0.15/0.32	0.05/0.76	0.10/0.52
β-Globulin	0.13/0.38	0.18/0.22	0.17/0.26
γ-Globulin	0.19/-0.15	0.38/-0.10	0.25/-0.13
ESR	0.60/0.08	0.78/0.04	0.65/0.07

C3 = complement component 3, C4 = complement component 4, CH<sub>100</sub> = total hemolytic complement, ESR = erythrocyte sedimentation rate.

\*Significant correlation at P<0.05.

ment but also to diaphragm dysfunction, which does not cause alterations in lung epithelial permeability. However, because many clinical and laboratory variables were studied, we cannot rule out the possibility that the number of subjects included was not sufficient to detect the presence of a difference.

This study demonstrated that the pulmonary clearance of <sup>99m</sup>Tc-DTPA is increased in SLE patients with active disease even without overt respiratory symptoms or chest X-ray abnormalities. Prospective studies are necessary to further evaluate the clinical usefulness of this observation.

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