

# Lung clearance of $^{99m}\text{Tc}$ -DTPA in ankylosing spondylitis

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## Abstract

The association of ankylosing spondylitis (AS) and lung parenchyma abnormalities has been shown in previous studies by radiological and pulmonary function tests. Technetium-99m diethylene triamine pentaacetic acid ( $^{99m}\text{Tc}$ -DTPA) dynamic lung scanning is an easy, noninvasive method to assess alveolar-capillary barrier permeability. We aimed to study the abnormalities in pulmonary clearance of  $^{99m}\text{Tc}$ -DTPA in patients with AS, and the presence of any correlation between this clearance and the radiological and pulmonary function tests. We studied twenty-one nonsmoker patients with AS who were compared to 21 age and sex matched healthy volunteers. All subjects underwent pulmonary function tests and pulmonary scintigraphy with  $^{99m}\text{Tc}$ -DTPA to evaluate pulmonary clearance. Clearance half time ( $T_{1/2}$ ) of  $^{99m}\text{Tc}$ -DTPA through the lungs was calculated by placing a monoexponential fit on the 30 min activity curves. High resolution CT and pulmonary function tests were performed for each patient. Our results showed the following: Spirometric parameters of forced vital capacity (FVC) and the ratio of forced expiratory value in 1sec/FVC (FEV1%) scores were worse in patients compared to the control group ( $P < 0.005$  and  $P < 0.05$ , respectively). Clearance half time was longer in AS group than in the control group ( $58.45 \pm 7.59$  and  $51.62 \pm 4.79$  min, respectively;  $P < 0.05$ ). There was a negative correlation between  $T_{1/2}$  value and FEV1% ( $r = -0.876$ ,  $P < 0.01$ ), of AS patients and the control group. Additionally, there were moderate positive correlation between  $T_{1/2}$  and FVC ( $r = 0.705$ ,  $P < 0.001$ ), weak positive correlation between  $T_{1/2}$  and FEF<sub>2575</sub> ( $r = 0.493$ ,  $P < 0.05$ ), and  $T_{1/2}$  and DLCO ( $r = 0.444$ ,  $P < 0.05$ ). A positive correlation was found between the duration of the disease and  $T_{1/2}$  ( $r = 0.44$ ,  $P < 0.05$ ). In conclusion, longer  $T_{1/2}$  values and lower FVC values in nonsmoker AS patients may suggest not only the pulmonary involvement in AS but also the duration of the disease.

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## Introduction

Ankylosing spondylitis (AS) is a seronegative spondyloarthritis that affects primarily the axial skeleton, causing pain and progressive stiffness of the spine [1]. Many extra-articular features such as pleuropulmonary involvement and chest wall restriction may develop during the course of the disease [2]. Pleuropulmonary complications are known to have a late onset and are usually asymptomatic [3]. These complications include upper lobe fibroblastic disease, interstitial lung disease, pleural thickening and pleural effusion [1, 4, 5].

Previous studies on the abnormalities of the lung parenchyma of ankylosing spondylitis patients have been generally based on plain radiography, high resolution computed tomography (HRCT) and pulmonary function tests (PFT) [6]. Technetium-99m diethylene triamine penta-acetic acid ( $^{99m}\text{Tc}$ -DTPA) aerosol inhalation scintigraphy, which is a simple, sensitive and non-invasive test to assess the pulmonary epithelial membrane permeability, was used to predict pulmonary alveolar epithelial damage in many diseases [7, 8].

To our knowledge there is no study showing abnormalities in lung clearance that may be found together with pulmonary function test abnormalities in patients with AS. In this study we tried to identify abnormalities of pulmonary clearance of  $^{99m}\text{Tc}$ -DTPA in patients with AS, and any correlation between this clearance and the radiological and pulmonary function tests.

## Subjects and methods

### Population and design of the study

Twenty-one nonsmokers AS patients who were followed in the Physical Medicine and Rehabilitation Clinic of the University Hospital entered the study (Table 1). A standardized questionnaire was completed and a complete physical examination was performed by the same physician (S.O.) for all patients. Disease duration, measured from the onset of low back pain, the presence or absence of respiratory symptoms, smoking history, occupation history, his-

tory of tuberculosis infection or radiation treatment for AS were recorded for each patient. None of the patients in the study had a history of pulmonary disease including tuberculosis, prolonged inorganic dust exposure or hospitalization for pneumonia and none was in the active phase of AS.

**Table 1.** Demographic characteristics, PFT and scintigraphic findings of subjects

	Patient (n = 21)	Control (n = 21)	P value
Age	45.57 ± 8.86	44.1 ± 8.44	NS
Sex (M/F)	12/9	12/9	NS
FVC	85.78 ± 8.27	98.53 ± 11.63	<0.005
FEV1	78.20 ± 7.95	84.73 ± 10.61	NS
FEV1%	91.41 ± 7.37	86.00 ± 4.15	<0.05
FEF <sub>25-75</sub>	79.49 ± 12.97	86.91 ± 11.66	NS
T <sub>1/2</sub>	58.45 ± 7.59	51.62 ± 4.79	<0.05
Disease duration	5.33 ± 4.06		

PFT: Pulmonary function test, FVC: Forced vital capacity, FEV1: Forced expiratory volume in one second, FEV1%: The ratio of FEV1/FVC, FEF<sub>25-75</sub>: Forced expiratory flow between 25 and 75 percent of expiration, NS: Nonsignificant,

Twenty one healthy nonsmoker volunteers, age and sex matched, were also enrolled to the study as the control group (Table 1). All volunteers were older than 22 years, had not any known chronic disease, no respiratory symptoms at least 1 month prior to the study and their chest X-rays were normal.

The AS patients were evaluated according to the activity criteria. The term "active disease" require fulfilment of at least two of the following variables, previously described [9, 10]: a) Moderate or severe dorsal-lumbar pain. b) Dorsal-lumbar morning stiffness lasting more than 60 min. c) Presence of symptomatic peripheral arthritis. d) Erythrocyte sedimentation rate (ESR) greater than 30 mm (Wintrobe first hour). All of the AS patients had non-active AS findings according to these criteria.

All subjects within 36 hours of their inclusion in the study were submitted to ventilation scintigraphy with a radioaerosol of <sup>99m</sup>Tc-DTPA, a chest X-ray and clinical examination. They were also submitted to laboratory tests, for the determination of disease activity, pulmonary function tests (PFT) and laboratory tests to assess the acute-phase proteins. All tests started at the same time of the day for each subject.

The study protocol was approved by the Ethic Committee of Zonguldak Karaelmas University Hospital, and all subjects gave their informed written consent before they were included in this study.

### Aerosol lung scintigraphy

<sup>99m</sup>Tc-DTPA (Pentacis, Cis Bio, France) was chelated by introducing 1480 MBq of sodium <sup>99m</sup>Tc pertechnetate into 2-3mL of normal saline. Quality control of <sup>99m</sup>Tc-DTPA was performed using thin layer chromatography. <sup>99m</sup>Tc-DTPA was placed in the nebuliser reservoir of a commercially available system (Biodex, USA). Aerosols with a mass median diameter of 0.8μ were produced with an oxygen inflow of 9 liter/min.

The subjects inhaled the aerosol for 4-5 min at their normal tidal volume while seated and then were disconnected from the system. The subjects were placed supine over a gamma camera (ADAC-Argus, USA) with a low energy all purpose collimator and lung fields were imaged in the posterior projection (64x64 matrix). Clearance from lungs was measured for 30 min (1 min/frame) following termination of inhalation. Areas of interest of equal size were placed over the right and left lung and over a background area that is right lung outer region. Radioactivity was first corrected for <sup>99m</sup>Tc decay and plotted as a logarithmic function of time. An exponential line of best fit was determined by regression analysis and <sup>99m</sup>Tc-DTPA lung clearance rate was expressed as the pulmonary half-time (T<sub>1/2</sub>), calculated by the software (version 3.20), i.e., the time for the activity to decrease to 50% of its peak value.

### Pulmonary function tests (PFT)

A trained technician measured PFTs. The same chest physician (R.A.) evaluated the results. Pulmonary function testing included measurement of the forced expiratory volume in 1 sec (FEV1), forced vital capacity (FVC), The ratio of FEV1/FVC (FEV1%), the forced midexpiratory flow rate (FEF<sub>25-75%</sub>) and CO diffusion capacity (DLCO) using the single breath technique and correcting for lung volume and hemoglobin levels. Observed values were expressed as absolute values compared with individuals of similar sex, age, weight and height.

### Chest radiographs and high resolution computerized tomography (CT)

All chest CT's were taken before scintigraphy and at least in a week scintigraphic measurements were done. The following features were evaluated on CT images: parenchymal micronodules, parenchymal bands, interlobular septal thickening, ground glass opacity, mosaic pattern, bronchial wall thickening, bronchial dilatation, pleural thickening, emphysema and honeycombing. Bronchial wall thickness and bronchial wall dilatation were scored on a four-point scale (0, absent; 1, mild; 2, moderate; and 3, severe) as in other studies [6, 11-13]. In order to assess bronchial wall dilatation, bronchial lumen diameter was weighted with respect to the accompanying pulmonary artery. As there are no established criteria, bronchial wall and pleural thickening were based on a subjective reading. The films were read by the same radiologist (KMY).

### Statistical analysis

Mann-Whitney U test was used to compare radioaerosol clearance, and spirometric measurement for data. Spearman test was used for correlations. All analyses were performed using the statistical package SPSS 11.0 for Windows and a P value less than 0.05 was considered statistically significant. (Version 11.0, Chicago, Ill, USA).

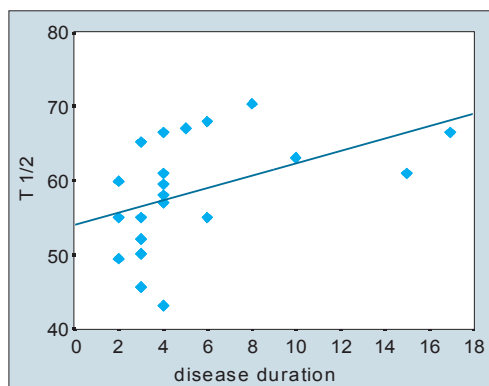
### Results

Demographic features, PFTs and scintigraphic findings of the groups are shown in Table 1. There wasn't any significant dif-

ference with regard to age and sex. The duration of illness was  $5.33 \pm 4.06$  years. Spirometric measurements such as FVC, FEV1%, FEF<sub>2575</sub> and DLCO scores were worse in AS group than in the control group ( $P < 0.005$  and  $P < 0.05$ , respectively).  $T_{1/2}$  was longer in AS group than in the control group ( $58.45 \pm 7.59$  and  $51.62 \pm 4.79$  min, respectively;  $P < 0.05$ ).

In our statistical analyses of spirometric measurements, there was a negative correlation between  $T_{1/2}$  value and FEV1% ( $r = -0.876$ ,  $P < 0.01$ ) of AS patients. Additionally, there were moderate positive correlation between  $T_{1/2}$  and FVC ( $r = 0.705$ ,  $P < 0.01$ ), weak positive correlation between  $T_{1/2}$  and FEF<sub>2575</sub> ( $r = 0.493$ ,  $P < 0.05$ ) and  $T_{1/2}$  and DLCO ( $r = 0.444$ ,  $P < 0.05$ ). A positive correlation was found between the duration of the disease and  $T_{1/2}$  ( $r = 0.44$ ,  $P < 0.05$  (Fig. 1).

$T_{1/2}$  values in relation to HRCT findings, disease duration and age, are given in Table 2. HRCT findings of the patients with AS were as follow: Mosaic pattern, bronchial wall thickening, ground-glass opacity (early inflammation), interlobular septal thickening, and parenchyma micro nodules frequently located in subpleural regions and the parenchyma bands. In our study, we found lung involvement in 12 of 21 patients (57 %) (Fig. 2A and B). In four of 21 AS patients, there were prolonged  $T_{1/2}$  values even HRCT findings were normal (Fig. 3).



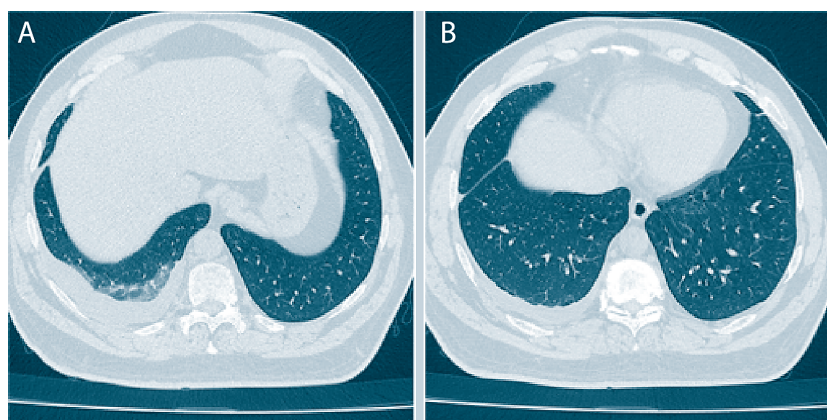
**Figure 1.** Correlation between  $T_{1/2}$  and disease duration

The hemi-logarithmic time-activity graph of <sup>99m</sup>Tc-DTPA radioaerosol scintigraphy from right and left lung fields and the dynamic ventilation imaging of a patient with AS are shown in Figures 4 and 5.

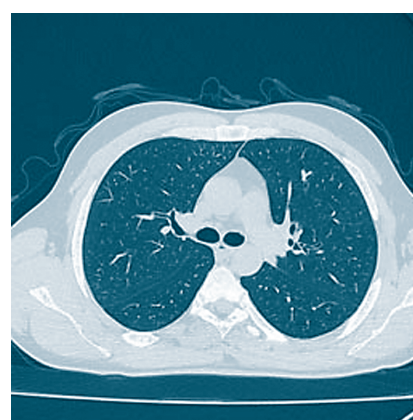
**Table 2.**  $T_{1/2}$  values in relation to HRCT findings, disease duration, and age

Patients No	Age	Disease duration	HRCT findings	$T_{1/2}$
1	29	6	Mosaic pattern, bronchial wall thickening, ground-glass opacity, interlobular septal thickening	49.35
2	39	5	Mosaic pattern, bronchial wall thickening	59.85
3	23	2	Mosaic pattern	70.35
4	55	15	Mosaic pattern	55.00
5	47	3	Bronchial wall thickening, parenchymal bands	55.00
6	46	4	-	66.50
7	56	2	Parenchymal micronodules	60.90
8	41	3	Mosaic pattern	43.05
9	50	10	Mosaic pattern, Parenchymal bands	59.50
10	23	4	-	45.50
11	32	2	-	50.00
12	47	4	-	65.10
13	35	4	-	67.00
14	52	17	-	58.00
15	43	2	Parenchymal bands	66.50
16	55	4	Parenchymal micronodules, ground-glass opacity	68.00
17	50	4	-	55.00
18	46	8	-	52.00
19	40	6	Parenchymal micronodules	63.00
20	54	3	-	60.90
21	54	3	Interlobular septal thickening	57.00

HRCT: High resolution computerized tomography

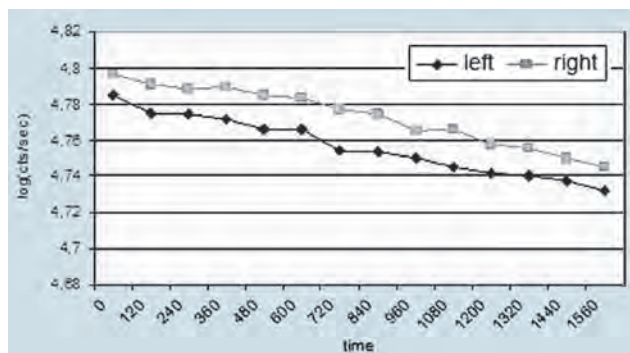


**Figure 2A.** A 39-years old male. A ground glass appearance with pleural effusion in right lung posterior segment of lower lobe is seen in the high resolution CT images of thorax. **2B.** Bilateral peribronchial thickenings in posterobasal segments, interstitial septal thickenings with pleural effusion in right lung, bilateral micronodular lesions, parenchymal band in left lung anterior segment of lower lobe is seen in the same patient.



**Figure 3.** prolonged  $T_{1/2}$  in a AS patient (Patient 13) having normal high resolution CT image.





**Figure 4.** The hemi-logarithmic time-activity graphy of  $^{99m}\text{Tc}$ -DTPA radio-aerosol scintigraphy from right and left lung fields of a patient with AS.

## Discussion

The alveolar capillary barrier is composed of the pulmonary surfactant system, the alveolar epithelium, the basement membrane and the capillary endothelium. This barrier allows free diffusion of gases but limits the transfer of water and solutes between alveoli and the blood. Clearance of inhaled radiolabelled tracer substances such as  $^{99m}\text{Tc}$ -DTPA from the lungs has been used to study the functional integrity of the alveolo-capillary barrier. Inhaled  $^{99m}\text{Tc}$ -DTPA passes through alveolo-capillary barrier to blood circulation and is excreted from the body by the renal system. Any condition affecting this barrier may change permeability [14]. Thus the clearance rate of  $^{99m}\text{Tc}$ -DTPA may show differences in diseases such as adult respiratory distress syndrome, sarcoidosis, idiopathic pulmonary fibrosis, cocaine addiction, pulmonary disease due to smoking, bleomycine intoxication, diabetes mellitus, exposure to welding fumes or allergic alveolitis [15-23]. The clearance rate of inhaled  $^{99m}\text{Tc}$ -DTPA from the alveolar space to blood provides an index of pulmonary epithelial permeability [24], and it has been previously used to detect early lung disease in collagen vascular diseases [25, 26].

Lung involvement in patients with AS is reported to be 1.3% - 73% in different studies depending on the radiological method used [1-3, 24, 27, 28] but as far we know there is no study that measures pulmonary alveolar epithelial permeability in AS patients.

In this study we attempted to identify changes in pulmonary alveolar epithelial permeability due to fibrosis or active interstitial inflammation of the lungs in patients with AS, by using  $^{99m}\text{Tc}$ -DTPA aerosol lung scintigraphy. We found a statistically significant difference between patients with AS and control subjects. This finding is similar like in the diseases affecting the lung parenchyma [1-3, 24, 27, 28]. Longer  $T_{1/2}$  values and lower FVC values plus the other spirometric parameters (FEV<sub>1</sub>%, FEF<sub>2575</sub>, DLCO) showing parenchymal disorder in patients with AS may suggest decreased pulmonary alveolar epithelial permeability due to fibrosis or active interstitial inflammation in patients with AS.

The connective tissue disorders affecting the lung and the mechanism leading to an increase in pulmonary permeability are not well known [29-32]. However, Foster et al.(1997) sug-



**Figure 5.** Dynamic ventilation imaging of the patient in Figure 2. The first three images on the upper row are taken in the first 3 min and the images in the lower row were taken in the last 3 min of the 30 min dynamic ventilation imaging.

gested the following explanations as possible reasons for the lag of clearance of  $^{99m}\text{Tc}$  DTPA from the lungs: 1) After deposition, dissociation of the  $^{99m}\text{Tc}$  label from the DTPA chelate and adherence of the label to intracellular or extracellular elements prevents clearance; 2) After clearance through the respiratory epithelium and passage into the pulmonary circulation, a redistribution within pulmonary tissues occurs; and 3) phagocytosis and retention of  $^{99m}\text{Tc}$  DTPA within parenchymal cells and/or the lymphatic system slow clearance [33]. In another study it was found that lung inflammation together with pulmonary fibrosis caused by amiodarone toxicity showed a prolonged mean  $T_{1/2}$  values of pulmonary clearance [34]. In our study, there were parenchymal changes detected by HRCT in 12 of 21 patients with AS, but pulmonary fibrosis was not so prominent (Table 2).

Braga et al (1996) found an age related reduction in clearance in healthy nonsmokers, even in the absence of clinically detectable lung disease [35]. The disease duration and age of the subjects may also influence pulmonary clearance rate of  $^{99m}\text{Tc}$ -DTPA. HRCT allowed us to examine the entire lung parenchyma in a sizeable population of patients with AS by a method that has proven its superior sensitivity to plain radiography [6, 11]. Recent studies have shown that AS associated pulmonary pathologies may be as high as 70% [13, 27]. In our study, we found lung involvement in 12 of 21 patients (57%). Median age of the disease was about 5.4 years and the fact that lung involvement is a late complication of the disease may explain why our study population has a relatively low pulmonary complication.

In the present study, we also found that even when the high resolution chest CT is normal, abnormalities of  $^{99m}\text{Tc}$ -DTPA clearance may indicate lung disease at a still earlier stage. In our opinion the value of  $^{99m}\text{Tc}$ -DTPA scintigraphy and clearance as a utility to ascertain early pulmonary involvement needs further investigation.

We established a significant correlation between  $T_{1/2}$  and FEV<sub>1</sub>%. We think that this depends on the obstructive pathology in early stages of AS. These functional alterations may not be associated with radiographic changes and in most cases patients are completely asymptomatic. Since obstruction ap-

pears to be localized mainly to the small airways, it has been suggested that these functional changes may represent an early phase preceding the development of clinical and/or radiographic evidence of constrictive or follicular bronchiolitis.

*In conclusion*, to our knowledge this is the first study detecting changes on lung  $^{99m}\text{Tc}$ -DTPA clearance in patients with AS. We found longer  $T_{1/2}$  values and lower FVC values in nonsmoker AS patients suggesting dysfunction in pulmonary clearance. Further studies with larger series are needed to clarify the dysfunction in lung clearance in various groups of AS patients.

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