PULMONARY INVOLVEMENT IN SYSTEMIC SCLEROSIS: SIGNIFICANCE OF Tc-99m DTPA CLEARANCE RATE

Sistemik sklerozda akciğer tutulumu: Tc-99m DTPA klirens oranının anlamlılığı

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Summary: *In the evaluation of pulmonary epithelial membrane integrity, Tc-99m-diethylenetriamine pentaacetic acid (Tc-99m DTPA) aerosol scintigraphy has been safely used as a sensitive method. In this study, we aimed to investigate the role of Tc-99m DTPA aerosol scintigraphy in the early detection of pulmonary involvement in patients with SS. Seventeen women with SS, and seven healthy women were included in the study. None of the patients and controls were cigarette smokers. Mean disease duration of the patients was 6.7 ± 5.1 years (1-20 years). All the patients and controls underwent aerosol scintigraphy using Tc-99m DTPA (30 mCi), and half clearance rate (T1/2) was calculated. Half clearance rate of Tc-99m DTPA was measured as 54.20 ± 14.25 min in right lung and 58.89 ± 18.34 min in left lung of patient group and 79.67 ± 14.59 min in right lung and 78.4 ± 12.56 min in left lung of control group. Significant difference was observed between the half clearance rates of the patients and controls ($p<0.001$). There was no correlation among Tc-99m DTPA clearance rate, disease duration, pulmonary function test, and X-ray abnormalities. This study showed that asymptomatic patients with SS may frequently have abnormal Tc-99m DTPA clearance rate. We concluded that Tc-99m DTPA aerosol scintigraphy may allow early detection of subclinical pulmonary involvement in patients with SS.*

Key Words: *Lung, Scintigraphy, Systemic sclerosis, Technetium Tc-99m diethylene etiriamine pentetate*

Özet: *Tc-99m dietilentriamin pentaasetik asid (Tc-99m DTPA) aerosol sintigrafisi, pulmoner epitelyal membran bütünlüğünün değerlendirilmesinde sensitif bir metod olarak güvenle kullanılmaktadır. Biz bu çalışmada, sistemik sklerozlu hastalarda pulmoner tutulumun erken tesbitinde Tc-99m DTPA aerosol sintigrafinin rolünü araştırmayı amaçladık. Çalışmaya, sistemik sklerozlu 17 kadın hasta ve yedi sağlıklı kadın dahil edildi. Hasta ve kontrol grubundan hiç kimse sigara kullanmıyordu. Hastaların ortalama hastalık süresi 6.7 ± 5.1 yıl idi. Hasta ve kontrol grubundaki bütün kişilere 30 mCi Tc-99m DTPA aerosol sintigrafisi çekildi ve aerosolün pulmoner yarı klirens hızı (T1/2) hesaplandı. Yarı klirens hızı hasta grubunda sağ akciğerde 54.20 ± 14.25 dakika ve sol akciğerde 58.89 ± 18.34 olarak, kontrollerde ise sağ akciğerde 79.67 ± 14.59 ve sol akciğerde 78.4 ± 12.56 olarak ölçüldü. Hasta ve kontroller arasındaki fark anlamlı bulundu ($p<0.001$). Tc-99m DTPA klirens hızı, hastalık süresi, solunum fonksiyon testi ve akciğer grafisi anormallikleri arasında korelasyon mevcut değildi. Bu çalışma, sistemik sklerozlu asemptomatik hastaların sıklıkla anormal Tc-99m DTPA klirens hızına sahip olabileceğini göstermiştir. Biz, Tc-99m DTPA aerosol sintigrafisinin, sistemik sklerozlu hastalarda asemptomatik akciğer tutulumunun erken tesbit edilebilmesine imkan sağlayabileceği sonucuna vardık.*

Anahtar Kelimeler: *Akciğer, Sintigrafi, Sistemic sclerosis, Technetium Tc 99m pentetate*

Systemic sclerosis (SS) is a generalized disorder of connective tissue characterized by fibrosis and degenerative changes in the blood vessels, skin, synovium, skeletal muscle, and certain internal organs, notably the gastrointestinal tract, lung, heart, and kidney (1). Postmortem examinations have shown evidence of pulmonary involvement in 70% to 100% of cases, and pulmonary involvement is the most common cause of death (2-4). SS is a disease frequently associated with interstitial pulmonary involvement, but the clinical symptoms and radiologic abnormalities may occur lately.

Pulmonary epithelial permeability may be measured non-invasively by the inhalation of Tc-99m DTPA in the form of an aerosol. This method depends on the principle of passive diffusion of inhaled hydrophilic solutions of low molecular weight into the bloodstream through alveolar epithelium and capillary endothelium (5). If there

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is injury at intercellular junctions, epithelial permeability increases, and as a result of this, pulmonary clearance of radioactive solutions increases too. Tc-99m DTPA clearance rate thus provides an index of alveolocapiller junction integrity (6) in a wide variety of lung disorders such as hyaline membrane disease (7), interstitial lung disease (8), pneumoconiosis (9), allergic alveolitis (10), collagen vascular disease (11), fibrosing alveolitis (12), and smoking (5,13). The clearance rate of Tc-99m DTPA is held to be a sensitive and early indicator of ongoing damage in pulmonary interstitial disease (12).

In this study, the pulmonary involvement in our patients has been investigated by assessing clinical findings, chest X-rays, pulmonary function tests, and pulmonary aerosol scintigraphy with Tc-99m DTPA.

MATERIALS AND METHODS

Patients

This prospective study was carried out on 17 patients with SS. Systemic sclerosis was diagnosed according to the American Rheumatism Association's preliminary criteria for the classification of SS (14). All patients had diffuse cutaneous SS. The patients were assessed for pulmonary involvement by chest X-ray and pulmonary function test. Then, clearance rate of the patients were measured by aerosol scintigraphy with Tc-99m DTPA.

All patients were women with a mean age of 39.7± 13.6 years (age range: 13-60 years). As a control group, seven healthy women (mean age: 29.7± 4.7 years; age range: 22-36 years) were included in the study. There was no significant difference between the mean ages of the patients and controls ($p>0.05$). None of the patients and controls were cigarette smokers. Mean disease duration of the patients was 6.7± 5.1 years (1-20 years).

Tc-99m DTPA aerosol scintigraphy

Two milliliters of 740-1110 MBq (20-30 mCi) Tc-99m DTPA was placed into the Ventiscan II nebulizer system, and aerosol produced by passing 9 liter of oxygene per minute through the system. Patients in the sitting position inhaled the Tc-99m DTPA aerosol for 3 minutes at normal tidal breathing. The mean diameter of the aerosol produced in the nebulizer system was 0.9 micron. Immediately after the inhalation, dynamic thorax images were obtained in a posterior view using a digital gamma camera system (Camstar 4000, GE Medical Systems) equipped with a low-energy high resolution collimator. Scintigraphic data were recorded at 1 minute intervals in a 128x128 word matrix for a 30 minutes period. Regions of interest were manually drawn around each lung, and counts were corrected for radioactive decay. Data were processed to obtain time-activity curves. By this way, the half clearance rate (T1/2) of radioactivity from both lungs was calculated.

Pulmonary function testing

Spirometric measurements of lung volumes, flow indices and diffusing capacities were performed in all patients, except one patient (no:8). The results were considered as abnormal if lung volumes were less than 80% of predicted values and/or diffusing capacity was less than75%.

SPSS/PS statistical program and Student's t test were used for statistical evaluation.

RESULTS

Results of the study are shown in Table I,II. Six patients with SS (35.3%) had dyspnea. Four patients (23.5%) manifested with rales at the end of inspiration. In pulmonary function test, one patient was excluded because of xerostomia (no:8), eight of the remaining 16 patients (50%) had restrictive pulmonary disorder. Diffuse reticular appearance was detected in the lung radiograms of seven patients (41.1%). Mean Tc-99m DTPA half clearance rate (T1/2) was measured as 54.20 ± 14.25 min in right lung and 58.89 ± 18.34 min in left lung of patient group and 79.67 ± 14.59 min in right lung and 78.4 ± 12.56 min in left lung of control group. T1/2 value was considered abnormal when it was more than two standart deviation outside mean values obtained in the controls. Thus, in 11 patients (64.7%), clearance rate was accelerated compared with the controls (Figure 1,

2). When the mean half clearance rate of the patient group was compared with that of the control group, it was observed that there was a significant difference between the two groups ($p \leq 0.001$).

When Tc-99m DTPA findings were compared with clinical findings, physical examination, chest X-ray, and pulmonary function tests utilizing SPSS/PS statistical program; eight out of 11 symptom-free patients, seven out of 10 patients with normal lung radiograms, and five out of eight patients with normal pulmonary function test showed an increase in the clearance rate of aerosol scintigraphy.

Table I. Results of the patients with SS

Pat. no	Age (yrs)	Disease duration (yrs)	Sex	Symptom	PE	X-ray	PFT	T 1/2 (min) R Lung	T 1/2 (min) L Lung
1	32	5	F	+	+	+	+	55.4	71.1
2	31	9	F	+	-	-	+	93.4	96.5
3	27	1	F	-	-	-	-	57.8	56.5
4	49	3	F	+	-	+	+	67.5	46.4
5	47	6	F	-	-	+	+	48.0	46.5
6	25	1	F	-	-	-	+	49.5	98.0
7	30	3	F	-	-	-	+	39.4	44.0
8	13	7	F	+	-	-	np	50.0	56.6
9	50	5	F	-	-	-	-	55.0	69.7
10	40	6	F	-	+	+	-	45.4	37.6
11	53	9	F	-	-	+	-	37.2	36.5
12	51	2	F	-	-	-	-	50.6	52.5
13	20	2	F	-	-	-	-	50.0	63.5
14	55	10	F	-	+	+	+	75.3	73.2
15	60	20	F	+	-	+	-	62.7	62.8
16	47	10	F	-	-	-	-	45.0	44.4
17	45	15	F	+	+	-	+	39.2	45.4

PE: Physical examination, PFT: pulmonary function test, (-): normal, (+): abnormal, T1/2: time to half clearance, F: female, np: not performed, R: right, L: left

Table II. Results of the controls

	Patient (n=17) X ± Sd.	Control (n=7) X ± Sd.	t	p
Right Lung	54.20 ±14.25	79.67±14.59	3.9	< 0.01
Left Lung	58.89±18.34	78.40±12.56	2.5	<0.01

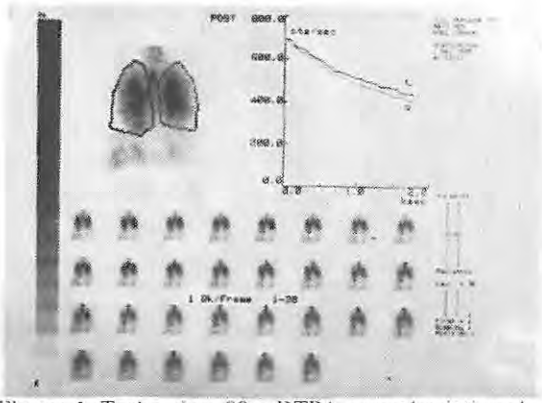

Figure 1. Technetium-99m DTPA aerosol scintigraphy of patient 11 (T1/2 right= 37.2 min, left= 36.5 min)

Figure 2. Technetium-99m DTPA aerosol scintigraphy of patient 12 (T1/2 right= 50.6 min, left= 52.5 min)

DISCUSSION

Systemic sclerosis is a chronic, multisystemic disorder frequently complicated by interstitial lung disease, which contributes significantly to the morbidity and mortality rate (15). Clinical symptoms of lung disease are not usually present when SS is first diagnosed.

Medical history, physical examination, chest X-ray, and pulmonary function test are important tools for the diagnosis of interstitial pulmonary disease. The initial clinical manifestations of interstitial lung disease are dyspnea, effort intolerance, and dry cough. Initially, the physical examination may not be revealing and auscultation of the chest may be normal. As the disease advances, dry rales, or coarse crackles on inspiration, are usually heard at the lung bases. The chest radiogram usually reveals patterns of diffuse reticular marking, prominent in the lower zones. Several radiographic patterns can be seen which correlate roughly with the duration of the disease. Total pulmonary capacity, vital capacity, and residual volume were found to be decreased in pulmonary function test. A restrictive respiratory functional pattern is usually present. In our study, six patients (35.2%) had positive history. Four patients (23.5%) had positive findings on pulmonary physical examination. Seven patients (41.1%) had reticular appearance in their lung radiograms. Eight of our patients (50%) showed similar abnormal finding in their respiratory function tests.

The clearance rate of a solute from distal airway is dependent on several factors related to properties of both solute and lung. Small lipophilic molecules, such as hexamethylpropylene amine oxime, are cleared very rapidly as a result of their ability to cross the epithelium by direct cellular penetration(16). Since their removal rate is perfusion-dependent, they have no value for the determination of epithelial integrity in the setting of radiolabelled solute clearance studies. Hydrophilic solutes, in contrast, exchange across the alveolar epithelium much more slowly at rates which depend on molecular charge and size. The pulmonary factors of potential importance in determining the rate of solute transfer, apart from disease itself, include regional surface area available for exchange, regional lung volume, intra-alveolar pressure, the composition and volume of the fluid in the alveoli, surfactant, and back-diffusion of solute from blood to lung interstitium (17).

In normal individuals, the clearance rate of Tc-99m DTPA is about 0.01 min^{-1}, or 1% per min (17). Several groups have shown that the rate of pulmonary clearance of Tc 99m DTPA is much faster in smokers than in non-smokers (5,13). The mechanism for the increased alveolar-capillary barrier permeability in smokers is not clear. It has been suggested that it reflects damage to the

alveolar epithelium(18), but also abnormal surfactant function in the alveoli (19). Schmekel et al. (20) reported that increased alveolar-capillary transfer of Tc-99m DTPA in smokers is not accompanied by increased transudation of small or large molecules into the alveoli. In their study, the findings supported the hypothesis that increased clearance of Tc-99m DTPA in smokers is related to surfactant dysfunction.

Corticosteroid treatment of lung involvement is more effective when started early (21). Therefore, sensitive and noninvasive methods, such as bronchoalveolar lavage and high resolution computed tomography (HRCT), are needed to detect subclinical pulmonary involvement in SS (22,23). In numerous previous studies, it was demonstrated that Tc-99m DTPA clerance rate was a highly sensitive and early indicator of interstitial pulmonary injury (15, 24). Previous studies have already showed a rapid Tc-99m DTPA clearance rate in cases affected by SS with clinical or roentgenographic evidence of interstitial lung disease (25, 26). Similarly, in our study, eight symptom-free patients, nine patients with normal physical examinations, seven patients with normal lung radiograms, five patients with normal pulmonary function test came up with the sign of pulmonary injury in Tc-99m DTPA aerosol scintigraphy. In 11 patients, clearance rate (T1/2) was increased compared with the results of the healthy controls.

In a previous study, whether a rapid clearance may indicate a nonspecific increase in epithelial permeability rather than subclinical fibrosing alveolitis was investigated (23). In this study, patients with an abnormally increased clearance rate underwent HRCT to evaluate parenchymal lung damage in SS, and it was found that the HRCT findings were consistent with early interstitial disease in all patients. Thunberg et al. (27) reported that no relationships were found between DTPA clearance rates and inflammatory markers (lymphocytes, albumin) in the bronchoalveolar lavage fluid in patients with sarcoidosis.

In conclusion, in SS patients, Tc-99m DTPA aerosol scintigraphy may be recommended as a simple, relatively inexpensive, and noninvasive test for the early diagnosis of pulmonary injury. Thus, proper treatment of lung involvement may be more successful in the light of early diagnosis.

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