Pulmonary Function Test in Rheumatoid Arthritis Patients

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Abstract- Lung disease is a common and important contributor to morbidity and mortality in rheumatoid arthritis (RA) patients. Studies have shown that diagnostic methods can reveal hidden pulmonary diseases even in RA patients with no respiratory symptoms. In this study, we assessed pulmonary function tests (PFTs) and chest radiographs (CXRs) in RA patients with more than three years of illness to find a suitable instrument for prospecting RA-induced lung diseases. We conducted a prospective cross-sectional study on 57 RA patients. Demographic, clinical, and CXR data were recorded. Residual volume (RV), total lung capacity (TLC), forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), and FEV1/FVC ratio was assessed. According to the FEV1/FVC ratio, patients were divided into three groups: FEV1/FVC below 70% (obstructive pattern) in 5% and between 70% and 85% (normal) in 50%, and above 85% (restrictive lung disease) in 45% of RA patients. Normal X-ray was the most common finding in CXR, and only cystic changes and reticular changes were found in 5% of patients. Analysis showed a significant relationship between abnormal chest images and the duration of disease (P=0.025), but PFT data did not result in any significance. Respiratory symptoms or clinical examinations are positive findings in the evaluation of asymptomatic patients, and using PFT is more rational than CXR. Our data show that there is no correlation between the disease duration and PFT data; hence, asymptomatic patients with a variety of risk factors should undergo further investigation.

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Keywords: Arthritis; Rheumatoid; Lung diseases; Pulmonary function tests

Introduction

Rheumatoid arthritis (RA) is a chronic, systemic, and inflammatory autoimmune disease that affects joints, cartilage, and bones and can lead to patient disability (1,2). The prevalence of RA is about 0.46% (3). Although RA has a lower prevalence in developing countries, assessing the prevalence of RA in Tehran (2014) showed that 0.33% (CI: 0.22%-0.46%) of people in Iran have the disease (4). RA damages organs and affects body systems. Among these extra-articular manifestations, lung disease is a common and important contributor to morbidity and mortality (5,6). Pulmonary manifestations of RA reflect upon chronic immune activation, immunomodulatory medications, infection, and even biological therapies. In RA, respiratory symptoms are due to a variety of conditions that affect the parenchyma, pleura, airways, or vasculature. They consist of parenchymal disease (interstitial lung disease (ILD)), pleurisy, airways, and vasculature disease (vasculitis and pulmonary hypertension) (5,7-9). Difficulty in diagnosis and the considerable mortality of RA-induced lung disease is a serious concern for clinicians in RA and is critical in improving disease progression (10,11)

Diagnostic methods such as pulse oximetry, chest radiography (CR), computed tomography (CT), and pulmonary function tests (PFTs) can reveal hidden pulmonary diseases (5,7,10,12). Some prospective observational studies assessed these relevant diseases; for example, Kawasaki assessed simple diagnostic methods on 246 RA patients in Brazil and showed that these methods could yield disease information even in RA patients with no respiratory symptoms (13). In other studies in Spain and Egypt, it was shown that in patients with early RA (joint symptoms less than 2 years), lung disease could be assessed by PFTs (14,15). In our

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country, an old study in 2011-2012 in Rasht showed a significant relationship between the disease activity rate and PFT (16). In the current study, we sought to assess PFTs in RA patients with more than three years of illness who had no respiratory symptoms. It was investigated whether chest radiography (CR) can be as good as PFTs in predicting RA-induced lung disease. The other important point is that methotrexate (MTX), as the common treatment for RA patients, is a specific drug-induced lung disease component (17,18). We assessed the effect of this drug on PFTs in our patients.

Materials and Methods

Patients' collection

In this cross-sectional study, we conducted a prospective cross-sectional study on patients with RA who were undergoing regular follow-up evaluations in the rheumatology clinics of Hafez and Motahari, Shiraz, Iran (May 2018-January 2019). The inclusion criteria were a confirmed diagnosis of RA made by a rheumatologist according to the 2010 American College of Rheumatology/European League (19). Patients with RA who had filed written informed consent were included in our study. Patients were excluded from the study if they had another inflammatory arthropathy, were pregnant, had a recent pulmonary infection, were unable to perform spirometry maneuvers, or did not complete the required tests. The Local Ethical Committee approved this study (IR.SUMS.MED.REC.1397.s13), and informed consent was obtained from the participants.

Demographic and clinical data (age, sex, time from disease onset, smoking status, drug usage history, and systemic and pulmonary symptoms) were recorded. All patients were referred for CXR and body plethysmography.

PTFs assessments

Residual volume (RV), total lung capacity (TLC), and forced vital capacity (FVC) were assessed by a ZAN 500 body plethysmograph, nSpire Health, Inc. The forced expiratory volume in the first second (FEV1) and FEV1/FVC ratio were also measured.

Statistical analysis

For the statistical analysis, the statistical software IBM SPSS Statistics for Windows version 21.0 (IBM Corp. 2012 was used. Armonk, NY: IBM Corp.) was used. Parametric data are expressed as the mean (±SD), and nonparametric data are described as the median and interquartile range (IQR). Quantitative data were analyzed using t-tests, qualitative data were analyzed using the chi-square test, and a $P<0.05$ was considered statistically significant. Categorical data were expressed as percentages. The Pearson product-moment correlation coefficient was used to measure the strength of the associations.

Results

Patients characteristics

Fifty-seven patients with RA were included in this study with a mean age of 55.25±1.2 years. In total, 93% of our patients were women. The mean duration of their disease was 135.6 months or 11 years, and 3.5% of patients had a history of smoking. In terms of pulmonary symptoms, 1.7% of patients occasionally complained of dry cough. Patient history showed that 14% had diabetes, 16.7% had hypertension, and 3.5% had cardiovascular disease (Table 1).

Drug use history showed that 90% of patients used corticosteroids (CS), 75.43% used methotrexate, and 3.5% took biological drugs. Laboratory assessments showed that 19.3% of patients had high ESR, and 26.4% had high CRP (Table 1).

Respiratory data

The symptoms and respiratory findings of the patients are listed in Table 2. According to the FEV1/FVC ratio, patients were divided into three groups. FEV1/FVC below 70% was considered an obstructive pattern, FEV1/FVC between 70% and 85% was considered normal, and FEV1/FVC above 85% was considered restrictive lung disease. Accordingly, 5% of patients had an obstructive pattern, 50% of patients had a normal pattern, and 45% of patients had a restrictive pattern in the pulmonary function test (Table 2).

Based on CXR data, normal X-ray was the most common finding in CXR patients, and only cystic changes and reticular changes were found in 5% of patients. In patients with abnormal CXR, 13% of patients had a normal pattern, and 11% had a restricted pattern (Table 2), but there was no significant relationship between the lung function test and chest X-ray ($P=0.785$) (data not shown).

Table 1. Demographic characteristics of the patients

Total number		**57**
Gender	**male**	7%
	female	93%
Age		55.25±1.2
BMI		28.9±5.5
Disease duration		135.6 ±86
Smoking	**smoker**	2 (3.5%)
	non-smoker	98(96.7%)
Respiratory symptoms and signs	**cough**	1 (1.7%)
	dyspnea	0 (0%)
	chest pain	0 (0%)
Disease	**diabetes**	8(14%)
	hypertension	10(17.5%)
	cardiovascular disease	2(3.5%)
renal disease		0(0%)
malignancy		1(1.7%)
Drug use	**Corticosteroids**	6(10%)
	methotrexate	43(75.43%)
	biologic treatments	2(3.5%)
Inflammatory MARKERS	**ESR**	46(80.7%)
	CRP	42(73.6%)

Table 2. PFT and CR findings

Spirometry	**FVC (predicted %)**	91.48±16.48
	FEV1 (predicted %)	61.93±16.7
FEV1/FVC (%)	**<70%**	5%
	70% to 85%	50%
	>85%	45%
FEF 25-75 %		83.05±23.93
Lung volumes	**TLC (predicted %)**	93.75±16.13
	VC (predicted %)	93.85±17.42
	RV (predicted %)	100.45±34.38
CXR	**Normal**	53%
	Bronchial thickening	1%
	Cystic changes	3%
	Reticular changes	3%

The correlation between RA duration and pulmonary data

Our analysis showed no significant relationship between ESR, CRP, and drug usage with lung involvement in this study. The results of statistical analysis showed only a significant relationship between abnormal chest images and the duration of the disease (P=0.025), indicating that the longer the duration of the disease, the more likely chest imaging is to be abnormal (data not shown). Otherwise, analyzing the correlation between disease duration and PFT data did not reveal any significant correlation (Figure 1). Comparing the correlation of PFT data of patients who used MTX with other patients did not show any significance (Figure 2) .

The correlation between drugs and pulmonary data

The percentage of patients who had the obstructive disease was less than 10% in all drug groups, but the rate of restrictive disease according to FEV1/FVC was more than 25% in all groups. Analysis showed that more than 50% of patients who used MTX and corticosteroids had restrictive disease (Table 3). There were no patients who used only biological drugs, and the combination with other drugs was only used by 2 patients.

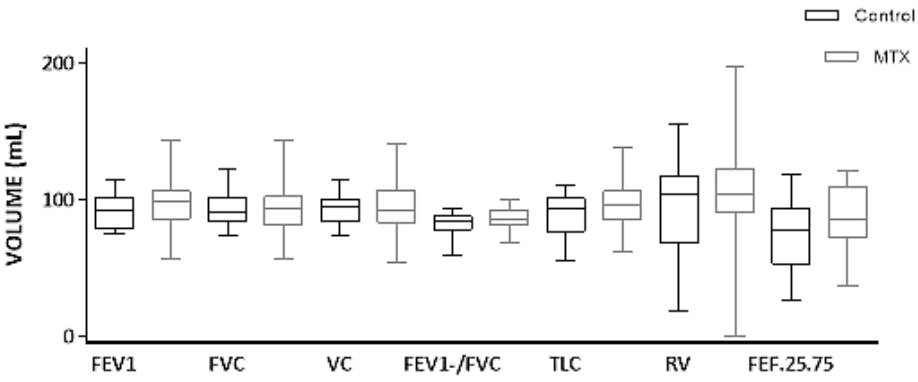

Figure 1. Pulmonary function test values according to disease duration

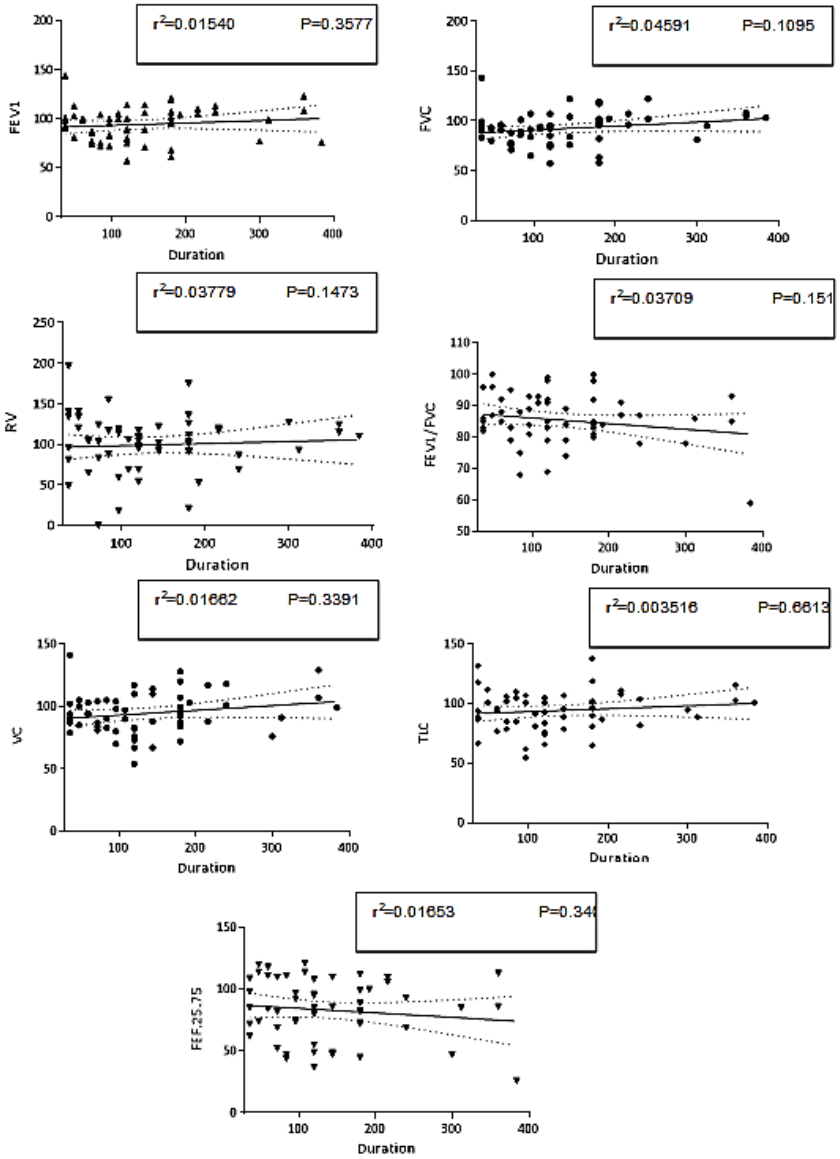

Figure 2. Pulmonary function tests were compared between patients who used methotrexate (MTX) and the control group

Table 3. FEV1/FVC data according to different drugs

		CS (n=13)	MTX (n=4)	CS+ MTX (n=39)	Biologic drug (n=0)	Non (n=2)
FEV1/FVC (%)	**<70%**	1 (8.33%)	0	2 (5.12%)	0	
	70% to 85%	7 (58.33%)	3 (75%)	17 (43.59%)	0	1 (50%)
	>85%	4 (33.33%)	1 (25%)	20 (51.28%)	0	1 (50%)

Discussion

Patients with RA have a median survival of 9.9 years, but the standardized mortality ratio of patients with the pulmonary disease compared to patients with only RA is 2.86, and the majority of respiratory manifestations occur within the first 5 years of disease (20,21). There are a variety of pulmonary manifestations of RA, and investigating the incidence of RA with pulmonary disease allows us to control the disease and increase life expectancy (5,22). Due to difficulty diagnosing it and the considerable mortality rate (one in 10 patients), there is a serious concern for the diagnosis and clinical practice of pulmonary disease in RA patients (23-25). In 1948, the first article on the correlation between pulmonary disease and RA was published (26), and in recent years, several authors have reported the relevance of RA-ILD (6,12,14,22). In this study, in 57 patients with and without any pulmonary disease symptoms, we found a high risk of pulmonary disease, especially restrictive disease.

Many articles have studied lung involvement in rheumatoid arthritis, but they have merely explored how early pulmonary involvement occurs in rheumatoid patients (12,14,15). For example, Habib showed the incidence of pulmonary disease in RA patients with less than 2 years of illness. This study investigated pulmonary involvement in RA patients with a disease duration of fewer than 2 years using computed tomography (CT) and PFT. This study provided evidence in active RA patients with high DAS28 scores, seropositive patients with RA, and patients receiving steroids and anti-TNFα therapy. They showed that pulmonary disease occurs early in the course of RA, and factors such as cigarette smoking and MTX are important risk factors (14). In another study, it was stated that 48.5% of patients with RA had the possibility of early airway obstruction, and their CT scan diagnosed airway involvement. According to this study, 33% of the patients with RA did not show dyspnea or cough, but they had a preclinical ILD, which was identified by an HRCT scan (27). Using chest X-rays and PFTs in 104 patients with RA showed abnormalities in 53.8% (30% pleural disease, 44% tuberculosis, and concomitant lung disease abnormalities 19.2%) (28), and in another study, PFT data detected lung abnormalities in 32% of patients, observing obstructive patterns in 20% and a restrictive pattern in 12% (28). All these data were assessed in RA patients in their early stages of the disease, and no other study has assessed these factors after a few years of illness.

Our study data showed that in patients with more than 3 years of illness, the symptoms are still present. Investigating the FEV1/FVC data showed that the percentage of patients with normal lungs was 50%, and 5% had hidden obstructive disease, while 45% of patients showed a restrictive pattern. Our study data are in agreement with other studies that showed that PFTs reveal a restrictive defect with low forced vital capacity (FVC), low total lung capacity (TLC) with or without low diffusion capacity of the lung for carbon monoxide (DLCO), and hypoxemia in RA patients (29-31). In this study, we did not omit patients who were occasional cigarette smokers because the rate of cigarette smoking among women in all previous studies in Iran was in the range of 1.3-5.9% (32).

Investigating the CXR data showed no correlation between CXR finding data and PFT. CXR has low sensitivity for the detection of pulmonary disease, and its efficiency in the early stages has been shown in several studies (33,34). However, some studies have evaluated CXR in patients with RA, which detected abnormalities in 19% to 29% (13,27,35), but earlier studies reported lower frequencies in only 1.6-6% of patients (36,37). To the best of our knowledge, no other study has investigated PFT and CXR in patients with long-term RA.

We identified several predictors for pulmonary diseases in patients with RA. Our PFT data provide evidence of the devastating impact of pulmonary disease amongst patients with RA to be more than three years. Assessing the correlation between the duration of RA disease and PTF data resulted in no significant findings. We showed that the duration of RA did not change lung volume and that other factors can affect the possibility of

pulmonary diseases.

Biologics and nonbiological anti-rheumatic drug efficacy are well established. MTX is the prototype of drug-induced lung toxicity in RA patients. MTX, as the main treatment for patients with RA (1% to 11% of RA patients use MTX), is related to the progression of RA-ILD (18,22). To eliminate the confounding effect of this drug, we compared the patients who used this drug with patients who received other treatments. We could not find any significant correlation, but the rate of patients with the restrictive disease who used MTX and CS was greater than that of the other groups. Our study showed that the highest rate of restrictive lung disease belonged to the MTX and corticosteroid groups, and the lowest rate belonged to the MTX group. This correlation between MTX and pulmonary disease has been proven in articles; for example, in a study on 15 cases and 36.5 months of follow up, the respiratory incidence rate was 0.45% (38), and in another study on 551 patients with RA, a 0.9% incidence was shown (39). Recently, in a meta-analysis by Conway, it was reported that MTX did not increase the risk of total adverse respiratory events, and there was no difference in the pulmonary death risk of patients taking MTX and those who did not (40). The other point is that several risk factors affect MTX pulmonary toxicity, such as age, rheumatoid pleura pulmonary involvement, diabetes mellitus, renal dysfunction, hypoalbuminemia, ANA positivity, or previous use of DMARDs. However, without knowing these factors and their role, we cannot decide on the real effect of MTX.

The total number of registered patients in our study was 57 patients with more than 3 years of illness. The results of our study support the issue that respiratory symptoms or clinical examination as independent parameters can have a positive effect, and in the evaluation of asymptomatic patients, using PFT is more rational than CXR. Our data also showed no correlation between disease duration and PFT data, but asymptomatic patients with multiple risk factors should undergo further investigation.

In the evaluation of rheumatoid arthritis patients, respiratory symptoms and chest examinations should be noticed, and using PFT is more rational than CXR. There is no correlation between the duration of duration and PFT findings; hence, asymptomatic patients with a variety of risk factors should undergo further investigation.

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