

Correlation of Lung Function with Disease Activity Rheumatoid Arthritis

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Abstract

Objectives: To find a correlation between Lung function with the disease activity in Rheumatoid arthritis.

Methods: The study was carried out on 40 (35 female and 5 male) patients with active RA who fulfilled the ARA 1987 revised criteria for the classification of RA. Patients with signs and symptoms of respiratory disease or chest injury were excluded from this study. The patients were all examine clinically by weighted and selective index of active of synovitis and assessed for functional status of the following; ESR, Hb % level pulmonary function tests including FEV1, VC, FEV1/ FVC and DLCO. Another group of 30 (27 female and 3 male) patients with active RA served as a control group.

Results: The results showed that Hb level ranged between (7-13.3 gm/dl), ESR ranged between 11-131 mm/hr and restrictive ventilatory defect was observed in 15 (37.5%) patients. Obstructive

ventilator defect was presened in 10 (25%) patients. And decrease DLCO was detected in 23 (51.5%) patients. There was a positive correlation between PETS with Hb%, ESR, Disease duration and activity of synovitis ($p < 0.05$).

Conclusion: The Lung function can be used to stratify abnormalities in a clinically useful manner and can be used as an indicator of disease activity in RA.

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Introduction

The first clinical description of Rheumatoid Arthritis (RA) is credited to Lander-Beauvais (Paris, 1800), but it was Alfred Baring Garrod (1859) who first used the term "Rheumatoid" arthritis.¹ Rheumatoid Arthritis (RA) is a chronic inflammatory, systemic disease that produces its most prominent manifestations in the dirhrodial joints.² The most common form of the disease is demonstrated by symmetrical, destructive and deforming polyarthritis affecting small and large synovial joints with associated systemic disturbances, in addition to a variety of extra-articular features and the presence of circulating antiglobulin antibodies (rheumatoid factor).³

The initial event inciting the inflammatory response is unknown. An infection's etiology of RA has been vigorously pursued without yielding convincing evidence, genetic and environmental factors control the progression, extent and pattern of the inflammatory response and thereby responsible for the heterogeneous clinical features.²

The disease has a global distribution and involves all ethnic groups. The prevalence varies from 0.3% to 1.5% worldwide,² while its prevalence in Iraq is 1%, it is 2.5 times greater in females than in males.^{2,4}

The physical examination of joints is considered to be pivotal in the assessment of RA disease activity; several articular indices have

been developed in attempt to standardize the clinical measurement of joint destruction. These indices were formulated on empirical basis and are fundamentally different in their construction. They include Ritchie articular index, American Rheumatism association index, Lunsbury index,⁵ and weighted and selective index.^{6,7,8} Other measurements of disease activity include the duration of morning stiffness, the patients assessment of pain (visual analog score), the patients global assessment of disease activity, the patients assessment of physical function (disability) and the acute phase reactant value namely: Erythrocyte Sedimentations Rate (ESR), C-Reactive protein (CRP) and hemoglobin concentration (Hb%).⁹

Pulmonary involvement is one of the most of common extra-reticular manifestation of RA and the second cause of death by infection.

Clinical symptoms of pulmonary insufficiency occur less frequently than the histological changes because RA imposes limitations that make physical exertion difficult, respiratory involvement may be asymptomatic. However, the mortality rate from pulmonary disease in RA is twice that of the general population.²

Pulmonary Function Tests (PFT_s) are widely used to

provide objective measures of Lung function for detecting and quantifying pulmonary impairment in cardio-pulmonary diseases and monitoring response to therapy or monitoring the effect of environmental, occupational and drug exposures-associated with Lung diseases.

After arterial blood gas measurement, the most common test of gas transfer across the Lung is the carbon monoxide diffusing capacity (DL_{CO}) also called transfer factor (TL_{CO}) which measures the rate of transfer of carbon monoxide (CO) from the Lung to the blood.¹⁰

Methods

This was across sectional study carried out at the unit of Rheumatology in Baghdad teaching hospital from October 2002 until March 2003. The sample consisted of 40 Iraqi patients (35 females and 5 males) with active Rheumatoid Arthritis as defined by the American Rheumatism Association ARA 1987 for the classification of RA.¹¹ Informed consent had been obtained from the patients. All the patients were life long non smoker's and with no evidence of respiratory diseases nor did they show any signs and symptoms (Cough, dyspnea, chest, pain, sputum production, cyanosis, oedema and clubbing) attributed to respiratory diseases.

The patients had no evidence of dry eyes or mouth, had no history of chest injury or exposure to radiation and had no chest infections three months prior to participating in the study. Assessment of disease activity was achieved by clinical and laboratory tests and pulmonary function tests; all of which were performed on the same day.

Step I

Clinical assessment was performed by weighted and selective index for activity of synovitis which depends on the degree of tenderness and swelling with weighted factor related to the joints' surface area, table 1 and 2 as this index- produces an excellent estimate of total joint inflammation, and is more sensitive in detecting changes in disease activity than any other indices.^{6,7,8}

The duration of morning stiffness and the presence of Rheumatoid nodules were reported. The patients' assessment for classification of functional status were recorded (disability), table 3 as well as information about treatment was obtained including the type of medication taken (Non steroidal Anti inflammatory drugs (NSAID) Corticosteroids and disease-modifying Anti Rheumatic Drugs (DMARD) and duration and regularity of intake were also noted.²

Table 1: Weighted and Selective Index for Activity of Synovitis

Joint	Weighted Factor (Related to Joint Surface Area)	Degree of Tenderness and Swelling (Scale 0 to 3)	Joint Score
Elbow			
R	48	-	-
L	48	-	-
Wrist			
R	32	-	-
L	32	-	-
MCP (Separately)			
R		-	-
L		-	-
PIP (Separately)			
R	5	-	-
L	5	-	-
Knee			
R	95	-	-
L	95	-	-
Ankle (Mortice)			
R	32	-	-
L	32	-	-
First MTP			
R	8	-	-
L	8	-	-
Second to fifth MTP separately			
R	5	-	-
L	5	-	-

R: Right; L: Left; MCP: Metacarpophalangeal joint; PIP: Paroximal Interphalangeal; MTP: Metatarsophalangeal joint

Table 2: Method of Scoring the Severing of Tenderness and Swelling of each Joint examined

Score	Tenderness	Soft tissues swelling
0	Not tender	None
1	Tender	Probable swelling
2	Tender, with wince	Definite swelling
3	Tender, with wince and withdraw response	Tense swelling

Table 3: Criteria for Classification of Functional Status in Rheumatoid Arthritis

Class	Functional Status in Rheumatoid Arthritis
Class I:	Completely able to perform usual activities of daily living (self-care, vocational, and a vocational).
Class II:	Able to perform usual self-care and vocational activities, but limited in a vocational activities.
Class III:	Able to perform usual self-care activities, but limited in vocational and a vocational activities.
Class IV:	Limited in ability to perform usual self-care, vocational, and a vocational activities.

Usually self-care activities included dressing, feeding, bathing, grooming, and toileting, while vocational activities are patient-desire and are often age and sex-specific.² They can include recreational and/or leisure activities at work, school, or domestic activities.

Step II

Laboratory assessment was performed by assessing the Erythrocyte sedimentation Rate (ESR), hemoglobin concentration (Hb %) and latex agglutination tests which took place in the teaching laboratories of Baghdad medical city.

Step III

Pulmonary function tests were performed at the pulmonary function unit in Baghdad teaching hospital by a senior technician.

Spirometry Parameters Include

The Forced Vital Capacity (FVC) test which was performed by having the patients inhale a Total Lung Capacity (TLC), then take maximum forced exhalation into a Spirometer. Traditionally, exhaled volume is measured as a function to indicate flow, but it can also be measured to illustrate the function of exhaled volume.

Forced Expiratory Volume in one second (FEV_1) is the volume of air expelled in the first second of a forced expiration starting from full inspiration, which is measured in liters.

The three primary spirometric indices in the forced test are FVC, FEV_1 and their Ratio FEV_1/FVC .

A minimum of the three vital capacity and forced expiratory volume determinations were performed and the two best values within 5% of each other were averaged. Spirometric measurements were considered abnormal when more than two residual Standard Deviates (SD) below the predicted value.

In terms of diagnosis, spirometry is used only to classify

patients as having normal air flow or obstructive or restrictive Lung disease.

The diffusing capacity for carbon monoxide (DL_{CO}) was measured using single breathing technique, which was performed as follows: The patient exhales to residual volume, a valve is open and the patient then inhales to full vital capacity. The test gas, which in addition to nitrogen contains 0.3% carbon monoxide an inert insoluble tracer gas Helium and 18-21% Oxygen. The patient relaxes into a breath-hold at total Lung capacity for 10 seconds and then exhales rapidly.¹⁰

The diffusing capacity for carbon monoxide corrected for hemoglobin and consider abnormal when more than two Standard Deviation (SD) below or above the predicted value.

A randomly selected sample group of 30 (27 females and 3 males) patients with inactive Rheumatoid arthritis matching for age and gender, served as a control group.

Statistical analysis of the data collected was performed using statistical packages for social science version 10.1 (Spss version 10.1).

The data were presented in simple measures of frequency, percentage, mean and SD.

The data was statistically analysed using the following tests:

1. Students- t test for the comparison of two means of quantitative data.
2. Chi. Square test (X^2) for comparison of qualitative data. p value of < 0.05 was used as level of significance.

Results

The study included 40 (35 female and 5 males) patients with active Rheumatoid Arthritis. The mean age was 37.5 ± 9.5 year (Ranging from 22-28 year). The mean disease duration was 6.6 ± 4.6 year (ranging between from 2-19 year). The demographical characteristic of the study patients with active RA are shown in table 4.

Table 4: Demographical Characteristic of Patients with active RA

Patients	Female	Male
Total number of patients 40	35	5
	87.5%	12.5%
Mean (range age in years) 37.5 (22-58)	37.8	35.2
	(22-55)	(22-58)
Mean (range) disease duration in years 6.6 (2-19)	6.8	5
	(2-16)	(2-8)

Ratio: Female: male = 7:1

The parameters of disease activity are shown in table 5.

Table 5: Parameters of Disease activity

Laboratory Test	Range	Mean	SD
Hb level (g/dl)	7-13.3	10.28	1.82
ESR level (mm/h)	11-131	53.77	27.53
Ar. Index	307-604	446	80.88

Hb: Hemoglobin; ESR: Erythrocyte Sedimentation Rate; Ar: Aortic regurgitation; SD Standard Deviation

All the study patients tested positive for the presence of Rheumatoid factors.. All the patients were found to belong to either class III or IV of functional classification. All the study patients experienced morning stiffness lasting more than one hour. None of the patients in either the study group or the control groups were smokers.

Pulmonary function tests abnormalities showed restrictive ventilator defect in 15 (37.5%) patients and obstructive ventilator defect in 10 (25%) patients.

The tests also showed decreased diffusing Lung capacity for carbon monoxide (DL_{CO}) in 23 (57.5%) patients.

Tables 6: Results of Pulmonary Function in Patients.

Function Test	Range	Mean	SD
FEV ₁ /Lit	(1.01-4.83)	2.21	0.88
FEV ₁ /FVC	28-219	78.55	30.43
FVC/lit	1.12-4.40	2.67	0.76
DLCO (mmol/min/kpa)	5.01-11.61	7.12	1.60

FEV₁: Forced Expiratory Volume; FVC: Forced Vital Capacity; DLCO: Diffusing Capacity of the Lung for Carbon Monoxide; SD: Standard Deviation

All the patients received treatment of non steroidal anti-inflammatory drugs, Cortico steroid and disease modifying anti Rheumatoid drugs.

The result of pulmonary function tests in study group and control group are show in Figure 1.

Table 7: Case –Control Comparison of PFTS defects in RA

PFTs Defect	Case N=40 No. (%)	Control N=30 No. (%)
Restrictive Ventilator defect	15 (37.5)	2 (6.6)
Obstructive Ventilatory defect	10 (25)	1 (3.3)
Decrease DL _{CO}	23 (57.5)	2 (6.6)

PFTS: Pulmonary Function Tests; DL_{CO}: Diffusing Capacity of the Lung for Carbon Monoxide

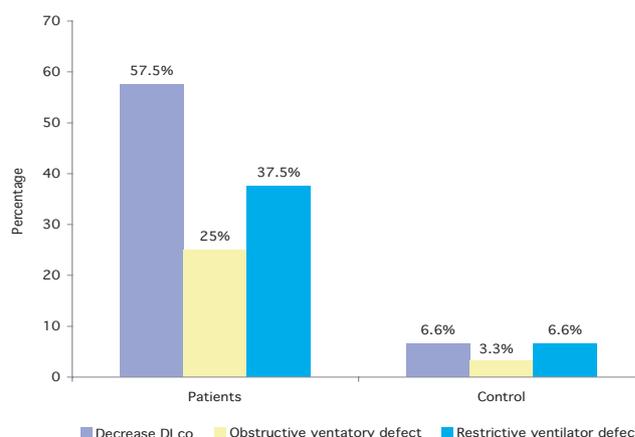


Figure 1: Bar chart show case-control difference in PFT abnormalities

Discussion

Spirometry is the most common and most useful of the lung function tests. It has extensive clinical implications . It is the least expensive test to perform and it should be the test most widely available in doctors' offices, clinics and hospitals.

The reduction in diffusing lung capacity of carbon monoxide reported was suggested to be an early indicator for the presence of both emphysema and interstitial fibrosis.¹⁰

A case report by Kawamura- T et al reported an incident of Rheumatoid Lung disease in which lung involvement preceded arthritis.¹²

This study was limited to patients with confirmed RA defined by ARA criteria with active disease, and all the patients in the study were free from respiratory signs and symptoms. Lung function tests are different from other medical tests in that many of them required patients to participate actively and vigorously. Since some patients would have been unable to perform the tests, the age of the study patients was limited to no more than 58 years old. It is widely accepted that RA is one of many chronic inflammatory diseases that is predominant in women, this was also reflected in this study where the female to male ratio was 7:1. This finding probably reflects the out patient population.

From analyzing the data obtained from disease activity parameters and pulmonary function tests in this cross sectional study of 40 active rheumatoid Iraqi patients (35 female and 5 males), the results demonstrated a definite correlation between FEV1 and FEV1/FVC with Hb% ($p=0.0001$) and an inverse relationship observed with ESR level and articular index and disease duration($p=0.0001$).

There was also a clear correlation between FVC and Hb% (0.0001) and inverse relation with ESR level and articular index and disease duration ($p=0.0001$) additionally DL_{CO} correlation with HB% and inversely with ESR level, articular index and

disease duration. ($p=0.0001$) when comparison of our study to V. saravanan et al¹³ study when they demonstrated clear correlation between FEF1 and Hb% ($p<0.01$) and borderline inverse relationship between FEF1 and ESR ($p=0.05$). Additionally DL_{CO} correlated with both HB% ($p=0.03$) and ESR($p=0.01$).

A study by Pelucchi-A et al confirms that Lung function and DL_{CO} in patients with juvenile arthritis are related to the clinical sub types of the disease and to the disease activity.¹⁴ The exact mechanism for the development of air way obstruction in RA is unknown, however, it is possible that the mucosal odema secondary to pre-existing air way inflammation may lead to bronchial narrowing and hence cause air way obstruction.¹⁵

The measurement of respiratory volumes and capacities is an essential tool for determining how well the lung is functioning.¹⁶ The decreased DL_{CO} measurement was indicative of pathology of pulmonary disease such as reduced lung surface area in Emphysema, altered structural component of alveolar-capillary membrane as is characteristic of Pulmonary Fibrosis or obstructed or obliterated pulmonary capillaries observed in Pulmonary Embolism.¹⁰

Vergnenegre et al¹⁷ recently reported a significant relationship between Forced Expiratory Flow (FEF 25-75), duration of articular disease, FEV₁/FVC and Ritchie index, and also a parallel evolution of pulmonary exacerbation and flares of articular disease in some patients⁽¹⁸⁾. The health assessment questionnaire (HAQ) disability index (DI) was also an important risk factor for the decline in both DL_{CO} and FVC.¹⁹

All the study patients were zero-positive for Rheumatoid factors, which suggests that there may be a significant positive correlation between the presence of Rheumatoid Factor (RF) and abnormal PFTS which agreement with other studies.²⁰ (this goes against previous statements where the author states that all the patients tested positive for the presence of rheumatoid factors)

A study by MC Donagh et al. reported that pulmonary function was often impaired in a pattern similar to that of advanced interstitial Lung disease.²¹ While in a study by Cannon GW et al, it was reported that Disease modifying anti Rheumatic drugs were observed to cause interstitial Lung disease.²²

Conclusions

1. Pulmonary function tests can be used as an indicator of disease activity in Rheumatoid Arthritis.
2. Lung function data can be used to stratify abnormalities in a clinically useful manner.
3. Longitudinal studies are needed to ascertain the effect of therapy on these abnormalities.
4. Overall, the results from this study demonstrated that the high incidence of pulmonary dysfunction observed in the study patients was unexpected and suggest that all patients with RA should undergo PFT_s for complete assessment.

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