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Pulmonary function test abnormalities in patients with rheumatoid arthritis: A single centre study

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ABSTRACT

Introduction: Pulmonary diseases are common extra-articular manifestations of rheumatoid arthritis (RA) and account for a high disease-related mortality. Pulmonary function tests (PFTs) are considered as one of the cost-effective options for the early identification of pulmonary involvement in RA. The objective of this study was to assess the prevalence of PFT abnormalities and its associated factors among diagnosed patients with RA visiting a tertiary care hospital in Sri Lanka.

Methods: A cross-sectional study was performed recruiting 42 consecutive RA patients attending the rheumatology clinic of Teaching Hospital Karapitiya, Galle, Sri Lanka (THK) in year 2018-2019. Data were collected using an interviewer-administered questionnaire. Lung functions were measured using spirometry. Mann-Whitney U test, the Spearman rank-order correlation coefficient and the Kruskal Wallis H test at 0.05 significance level were used to identify associations between variables.

Results: Out of all the patients (N = 42), 57.1% showed abnormal PFT results. Among them obstructive defect was noted in 16.6%, small airway defect in 37.5% and pure restrictive defect in 45.9%. No patients with combined restrictive and obstructive diseases were detected. A statistically significant association of forced vital capacity (FVC) with the presence of respiratory symptoms (p = 0.02) was detected. Statistically significant negative correlations were reported between peak expiratory rate (PFR) and age (r_s = -0.371, p = 0.01) and PFR and disease activity (r_s = -0.393, p = 0.01). Age, disease duration, disease severity and presence of respiratory symptoms showed no association with types of respiratory abnormalities.

Conclusions: PFT abnormalities were detected in considerable proportion of RA patients. PFTs should be performed in patients with RA, irrespective of the duration and the severity of disease or respiratory symptoms.

Key Words: *Pulmonary function tests, Pulmonary involvement, Rheumatoid arthritis.*

Introduction

Rheumatoid arthritis (RA) is a chronic multisystem disease of autoimmune nature, characterised by both articular and extra-articular manifestations. Pulmonary manifestations occur due to the involvement of airways, lung parenchyma, pleura or pulmonary vasculature which altogether accounts for around 60-70% of prevalence among the RA population (1). The lung involvement follows the articular disease and usually manifest within five years since the onset of symptoms, but sometimes it could be the first manifestation of RA (2,3). It is found that around 15% of RA-related mortality is due to lung disease with interstitial lung disease (RA-ILD) being the commonest (4,5). Airway involvement in RA mainly includes bronchiolitis, bronchiectasis, airway hyper-reactivity, obstructive small airway disease and cricoarytenoid disease (1). The reported prevalence of airways disease in RA is 39% to 60% (6-8) while it was highly variable for RA-ILD due to extensive heterogeneity among studies. Research done based on pulmonary function tests (PFTs) have found that small airway defects defined by low forced expiratory flow (FEF) 25-75% are more common among RA patients (7-9). Diagnosing and treating RA-lung disease has assumed more significance since drugs such as mycophenolate mofetil (MMF) and rituximab are now being used in treating them (10-12).

High-resolution computed tomography (HRCT) is currently recognised as the most sensitive investigation in diagnosing rheumatoid lung disease (1, 10). HRCT is not available widely and is costly. Therefore, it is important to find a cheaper and relatively widely available investigation to screen patients with RA to identify those who need HRCT. PFT, especially spirometry, is one such investigation that can help diagnose possible lung involvement and recommend further investigations. In a clinical setting, history and examination are usually used to identify the patients who need further investigations. Besides, symptoms like exertional dyspnoea are difficult to assess in patients with activity limiting joint disease.

The studies done to look for the possible risk factors have found a positive relationship of RA-ILD with advanced age, smoking, use of methotrexate (MTX), disease severity, disease duration and a score calculated according to joint involvement on plain X-rays named "Larsen score" (13,14). Contrary to this, some studies could not prove any relationship with the risk factors mentioned above (15, 16). For these studies done to determine the relationship, they have used PFTs together with radiological studies while most of the recent studies used HRCT as the indicator of lung involvement (13-16). There was no Sri Lankan study based on PFTs to assess pulmonary involvement in RA. The objectives of this study were to assess the prevalence of PFT abnormalities among RA patients visiting the Rheumatology clinic in a tertiary care hospital and to evaluate their relationship with clinical characteristics.

Methods

Patient recruitment

A cross-sectional study was conducted in the Department of Physiology, Faculty of Medicine, University of Ruhuna and the Rheumatology Clinic, Teaching Hospital Karapitiya. Forty-two consecutive patients attending the rheumatology clinic of THK from October 2018 to December 2019 and diagnosed with RA using 2010 ACR/EULAR Criteria (17) were included for the study. The Informed written consent was obtained from the patients by the principal investigator who was not involved in patient management at the clinic. Patients were informed that refusal to take part in the study would not affect their management and that they could consider withdrawing at any stage.

Patients suffering from long-term chronic lung diseases which have no apparent clinical relationship to RA, patients with occupational exposures known to cause ILD, patients with co-existing connective tissue disorders, patients on any drug that may cause lung involvement other than prescribed drugs for rheumatoid arthritis and pregnant and lactating females were excluded from the study.

Ethical clearance was obtained from the Ethics Review Committee, Faculty of Medicine, University of Ruhuna.

Clinical assessment

An interviewer-administered questionnaire was used to collect sociodemographic and disease related information from patients. Duration of the disease, disease-modifying drugs, smoking history with pack-years (one pack-year = 20/day for one year) and respiratory symptoms, current symptoms and signs of joint involvement, ESR (noted from clinic information) were documented under disease related information. Patient's self-assessment of global health was documented to calculate the disease activity score-28 (DAS-28). Using DAS-28 scoring system disease activity was categorised into four: score <2.6 = remission, score between 2.6 and 3.2 = low disease activity, score of > 3.2 up to and including 5.1 = moderate disease activity and score of > 5.1 = high disease activity.

Pulmonary Function Tests

A standard spirometer (*Spirolab III*™, Italy) was used for lung function studies. Tests were performed in the sitting position and the forced expiratory manoeuvre was repeated three times and the best or the highest readings were documented. Lung function studies mainly including forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), FEV1/FVC ratio and forced expiratory flow from 25% to 75% of FVC (FEF25–75) which is a specific index of small airway function and peak expiratory flow (PEF) were measured. All spirometry assessments were done and interpreted at the Department of Physiology, Faculty of Medicine, University of Ruhuna.

Based on the results of the PFTs, five groups were defined: Group 1 - Normal PFT; Group 2 - obstructive airways disease as defined by low FEV_1/FVC ratio; Group 3 - small airways involvement suggested by low FEF25–75% ratio in the absence of reduced FEV_1/FVC ratio and absence of restrictive syndrome; Group 4 - restrictive defect as defined by low FVC with a normal FEV_1/FVC ratio expressed in percentages; and Group 5 - a combined pattern defined as the coexistence of airway obstruction and restrictive syndrome. PFT abnormalities were categorised as abnormal if values were <70% of the predicted values adjusted for age, sex, and height.

Data were entered into an *MS Excel*™ worksheet and analysed using the *SPSS*™ software (version 21). The FEV1, FVC, FEF 25–75% and PEF were expressed as a percentage of the predicted values for each individual's age, sex, and height. Normality assessment was done before data analysis. Mean (SD) and median (IQR) were calculated for FVC, FEV1, FEF 25–75% and PEF within each category for disease duration and disease severity. Further, similar calculations were done for age, disease duration and disease severity within each type of respiratory abnormality. Mann-Whitney U test was used to compare the spirometric median values between the two groups of presence and absence of symptoms. A similar analysis was done between early and late diseases. Kruskal Wallis H test was used to compare the medians of age, disease duration and disease severity between respiratory abnormalities. Correlation of spirometric parameters with age, disease duration and disease severity were assessed using Spearman's rho. The level of significance was considered as 0.05.

Results

Characteristics of the study population

A total of 42 diagnosed RA patients attending Rheumatology clinic, THK fulfilling the 2010 ACR/EULAR Criteria for RA were recruited to the study. Approximately 86% were females (n = 36). The mean age (SD) of the participants was 57.7 (8.2) years, with an age range between 38 - 75 years. 9.5% of patients (n = 4) were past or present smokers with one having a history of less than ten pack-years of smoking and the other 3, 10 - 19 pack-years of smoking. Nearly 57% (n = 25) of patients complained of respiratory symptoms and among them, 80 % (n = 20) had mild exertional shortness of breath while only one patient complained of moderate shortness of breath at exertion. A minority of patients (n = 4, 16.0%) complained of dry cough. No other respiratory symptoms were reported. The mean duration (SD) of articular disease at the time of the study was 8.4 (7.6) years. The majority of the patients (n = 31, 73.8%) were on MTX at the time of participating in the study. Disease activity was calculated according to DAS-28 criteria and the mean (SD) value for the study population was 3.26 (0.76).

Among the participants 14.3% (n = 6) were in disease remission, 31% (n = 13) had low disease activity and 54.8% (n = 23) had moderate disease activity. Duration of disease, duration of treatment, ESR values and DAS-28 score were assessed under RA characteristics of the study sample (Table 1).

The FEV1, FVC, FEF 25-75% and PEF were expressed as the percentage of the predicted values for each individual's age, sex, and height under spirometric parameters of the study sample. Mean (SD) and median (IQR) were calculated for FVC, FEV1, FEF 25-75% and PEF (Table 2).

Description of PFT abnormalities

Out of all the patients (N = 42), 57.1% (n = 24) showed abnormal PFT results; obstructive defect (FEV1/FVC <70%) in 9.5% (n = 4), small airway defect (FEF 25-75 <70% without obstructive or restrictive disease pattern) in 21.4% (n = 9) and pure restrictive defect in 26.2% (n = 11). However, there were no patients with combined restrictive and obstructive diseases.

Respiratory symptoms and PFT

The spirometric parameters were compared with presence or absence of respiratory symptoms using Mann Whitney U test (Table 3). A statistically significant association was found between low FVC and having respiratory symptoms while no association was found with FEV1, FEF 25-75% or PEFR with respiratory symptoms.

Table 1: Rheumatoid arthritis characteristics of the study sample (N = 42)

Disease Characteristics	Mean (SD)	Median (IQR)
Duration of disease (in years)	8.4 (7.6)	6.0 (5.0)
Duration on treatment (in years)	7.7 (6.4)	6.0 (5.0)
ESR	24.2 (13.1)	20.0 (20.2)
DAS-28	3.26 (0.76)	3.5 (1.0)

* DAS-28 – Disease active score

Table 2: Spirometric parameters of the study sample (N = 42)

Spirometric parameter(% predicted)	Mean (SD)	Median (IQR)
FVC	84.7 (16.2)	87 (18.5)
FEV1	82.9 (18.7)	83 (21.5)
FEF 25 - 75%	81.1 (35.7)	72 (51.5)
PEFR	83.8 (20.9)	88 (25)

Table 3: Comparison of the spirometric parameters between the patients with and without respiratory symptoms (N = 42)

Spirometric parameter (% predicted)	Patients with symptoms (n = 25) Median (IQR)	Patient without symptoms (n = 17) Median (IQR)	Significance *p*
FVC	84.0 (18.0)	92.0 (16.9)	0.02*
FEV1	78.0 (13.0)	90.0 (35.5)	0.16
FEF 25 - 75%	72.0 (61.0)	72.0 (41.5)	0.51
PEFR	88.0 (19.7)	92.0 (30.0)	0.71

** Significant at p=0.05 significance level*

The majority (57.1%, n = 12/21) of patients with breathlessness showed respiratory abnormalities and among them 50% (n = 6) had restrictive lung defects while 41.6% (n = 5) had small airway defects. Among the four patients with non-productive cough two had small airway defects and the remaining two had restrictive defects. However, there was no significant association of either of the above symptoms with the type of respiratory abnormality.

Rheumatoid arthritis characteristics and PFT abnormalities

Nine out of 13 patients (69.3%) with low disease activity had respiratory abnormalities while thirteen (56.5%) patients with moderate disease activity showed abnormal tests. There was no statistically significant difference of the type or respiratory abnormalities with disease activity. Moreover, it was found no statistically significant association of any of the PFT abnormalities with disease duration. (Table 4).

It was unable to demonstrate any significant correlation of FVC, FEV1 or FEF25-75% with patient's age, disease duration or disease activity except a significant negative correlation between PFR with age (r_s = -0.371, p = 0.01) and disease activity (r_s = -0.393, p = 0.01) (Table 5).

Abnormal PFT and known risk factors

Among the 31 patients on MTX, 41.9% (n=13) had normal pulmonary functions and 58.1% (n = 18) had abnormal results. Eight of them had restrictive PFT results. However, neither of these groups had a statistically significant difference (p = 0.69). Only 4 out of the 42 participants were smokers and only one of them showed abnormal PFT suggestive of an obstructive defect.

Table 4: Association of the disease duration and severity with the type of respiratory abnormality

Disease Characteristics	Pulmonary Function Tests pattern				Significance *p*
	Normal PFT (n = 18) Median (IQR)	Obstructive defect (n = 4) Median (IQR)	Small airway defect (n = 9) Median (IQR)	Restrictive defect (n = 11) Median (IQR)	
Disease duration (in years)	7.5 (5.8)	11.5 (22)	4.0 (1.5)	6.0 (3.0)	0.061
Disease severity	3.6 (1.6)	3.2 (1.1)	3.6 (0.7)	3.5 (1.0)	0.645

Table 5: Correlation between age, disease duration, disease activity and Pulmonary Function Tests parameters (N = 42)

	PFT parameters - % predicted spearman's rho correlation coefficient (*p*-value)			
	FVC	FEV1	FEF	PFR
Age	-0.130 (0.41)	0.129 (0.41)	0.129 (0.41)	-0.371 (0.01)*
Disease duration	0.137 (0.38)	0.239 (0.12)	0.389 (0.48)	-0.096 (0.54)
Disease activity	0.211 (0.18)	-0.099 (0.53)	-0.049 (0.75)	-0.393 (0.01)*

** Significant at p=0.05 significance level*

Discussion

In this single-centre study on 42 diagnosed patients with RA, the patients were assessed clinically and with spirometry. The study was mainly aimed at identifying the prevalence of PFT abnormalities and their association with symptoms, disease duration and disease activity.

Since there is wide variability in the definition of the disease, study population, study design and diagnostic methods, the prevalence of PFT defects among RA patients shows poor consistency among the studies done in the past. However, PFT abnormalities are shown to be common among patients with RA (18,19). In the present study, 57.1%, of patients with RA showed defects in their PFTs. This is consistent with the previously reported 64% and 55.8% prevalences in Youssef *et al.,* and Bilgici *et al.*, respectively (18,19). Furthermore, in this study, among patients with PFT defects, the restrictive defects showed the highest prevalence (26.2%), which is a higher value compared to previous studies (19). The prevalence of obstructive airway defect defined by low FEV1/ FVC was 9.5%. There were no patients with a combination of the above two types of defects. In contrary to this, Youssef *et al.,* found mixed restrictive and obstructive pattern as the commonest defect which has been reported in nearly 31% of their patients while only 22.1% showed pure restrictive defects (18). However, in keeping with our study, Assadi *et al.*, in a study done in Oman, found that 37.5% of the highest prevalence of PFT defects were restrictive in nature. The picture was different in studies where HRCT findings defined RA-ILD. In a large population-based study done in the USA where they have based HRCT findings and compared them with PFTs, clinically significant RA-ILD has been observed only in 8 to 10% of patients (20). A Sri Lankan study done in a District General Hospital by Wickrematilake G has revealed the prevalence of ILD in RA to be 14.6% (21). However, in the latter study, HRCT was used for the diagnosis and patients were selected for HRCT after clinical assessment. Therefore, there is a possibility of not detecting patients without clinical features. Besides, findings on PFTs depend strongly on the patients' compliance and poor compliance would result in low FVC and FEV1 which is the pattern suggestive of a restrictive defect. Therefore, the true number of patients with a restrictive disease among our patients could be much less than detected. Further into this, the comparatively low prevalence of obstructive disease seen in our study could be due to the low percentage of smokers which is well proven to directly associate with airway disease (1).

Interestingly, our study showed a 21.4% prevalence of small airway defects defined by low PEF 25-75% in the absence of an obstructive or restrictive defect. Therefore, the prevalence of small airway abnormalities was much higher than the obstructive airway disease defined by low FEV1/FVC. The small airways which extend from 8th generation airways have smaller internal diameters, less than 2 mm. However, their total cross-sectional surface area is much greater than that of large airways. Moreover, it is considered a "silent zone" where disease can accumulate chronically over the years without manifestations. FEF 25-75% is considered as having high sensitivity for such asymptomatic and symptomatic disorders of small airways (22). In fact, Cortet *et al.,* who reported 14 % of patients with small airway defects in his study population of RA found that it is the commonest PFT defect (23).

Even though this study demonstrated a statistically significant association of symptoms with FVC, an association was not detected between symptoms and restrictive defect or any other type of respiratory abnormality. Contrary to our findings, Youssef *et al.,* found that respiratory symptoms such as dyspnoea and cough were predictive of an underlying lung abnormality detected by PFT (18). On the other hand, a study done in New Zealand failed to demonstrate any such association (3).

We found a statistically significant correlation of PFR with age and disease activity. Similar co-relation has been reported with age and disease severity in previous studies (19). However, our study showed no statistically significant association of any PFT defect type with duration or disease activity. In keeping with the present study, Perez *et al.*, and Wilsher *et al.*, failed to demonstrate any significant relationship between airways involvement on PFTs and clinical or immunologic features of RA (3,15). Contrary to this, Vergnenegre *et al.,* have concluded that PFT abnormalities were affected by the duration of the disease and FEV1/ FVC was affected by the disease activity as well (24).

Furthermore, a large prospective cohort study done by Sparks *et al.,* found that patients in high or moderate disease activity, defined by DAS-28, have a 2-fold increased risk of developing RA-ILD than those in remission or low disease activity (25). Since disease activity is a dynamic variable over the years, it is difficult to come into a conclusion by the disease activity of the patient at the time of the study. Therefore, further studies, especially longitudinal studies are important to assess the correlation of lung disease with variation in disease activity.

Our study comprised some limitations. We could not achieve the expected sample size of 76 due to the inability to perform lung function studies during COVID-19 pandemic. Furthermore, it was unethical to perform such studies with high risk of contamination for this patient population. Therefore, the analysis was done with 42 participants who had undergone study before the pandemic. In addition to this, the patients were recruited from a rheumatology clinic of a tertiary care hospital could introduce some bias due to the selection of patients with advanced disease status than that in the overall RA population. However, disease activity was mild to moderate in a significant proportion of the included patients at the time of pulmonary assessment. Besides, the small sample size in our study would not have represented the whole RA disease population. Furthermore, the lack of resources to perform more advanced pulmonary function studies such as plethysmography and carbon monoxide diffusion capacity has compromised the overall picture that PFTs could assess.

In conclusion, considering the above findings and the research evidence from other studies, it is evident that asymptomatic patients could have significant abnormalities in their lung function tests. Further, the disease activity or duration have not shown a significant correlation with PFTs. Moreover, the presence of symptoms could not determine their lung function abnormalities. Therefore, in order to identify the patients with lung involvement, it is better to do a PFT during the early years of onset of the articular symptoms irrespective of their disease activity or pulmonary symptomatology. Since spirometry is the cheapest and the most available study, it can be used as the initial step followed by HRCT, depending on the significance of the findings.

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