Pulmonary Functions Testing in Patients with Rheumatoid Arthritis

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ABSTRACT: **Background:** A high incidence of abnormal pulmonary function tests has been reported in cross-sectional studies among patients with rheumatoid arthritis. Few patients have been enrolled in longitudinal studies.

Objectives: To perform PFT in rheumatoid arthritic patients without pulmonary involvement and to identify variables related to changes in PFT over 5 years of follow-up.

Methods: Consecutive RA patients underwent PFT according to recommendations of the American Thoracic Society. All surviving patients were advised to repeat the examination 5 years later.

Results: PFT was performed in 82 patients (21 men, 61 women). Their mean age was 55.7 (15.9) years and the mean RA duration was 11.1 (10) years. Five years later 15 patients (18.3%) had died. Among the 67 surviving patients, 38 (56.7%) agreed to participate in a follow-up study. The initial PFT revealed normal PFT in only 30 patients (36.6%); an obstructive ventilatory defect in 2 (2.4%), a small airway defect in 12 (17%), a restrictive ventilatory defect in 21 (25.6%), and reduced DLco in 17 (20.7%). Among the 38 patients participating in the 5 year follow-up study, 8 developed respiratory symptoms, one patient had a new obstructive ventilatory defect, one patient developed a restrictive ventilatory defect, and 5 patients had a newly developed small airway defect. The DLco had improved in 7 of the 8 patients who initially had reduced DLco, reaching normal values in 5 patients. Over the study period a new reduction in DLco was observed in 7 patients. Linear regression analyses failed to identify any patient or disease-specific characteristics that could predict a worsening in PFT. The absolute yearly decline in forced expiratory volume in 1 sec among our RA patients was 47 ml/year, a decline similar to that seen among current smokers.

Conclusions: Serial PFT among patients with RA is indicated and allows for earlier identification of various ventilatory defects. Small airways disturbance was a common finding in our RA patients. *IMAJ* 2009;11:83–87

KEY WORDS: rheumatoid arthritis, pulmonary function tests, small airway disturbance, mortality

PFT = pulmonary function testing
RA = rheumatoid arthritis
DLco = CO diffusion capacity

Pulmonary involvement contributes significantly to morbidity and mortality of patients with rheumatoid arthritis and is the second most common cause of death, the first being infections [1]. It has been suggested that patients with RA may benefit from serial pulmonary function testing to allow early identification of pulmonary disease [2]. Several studies have reported that patients with RA have an increased incidence of abnormal findings in PFT. However, only two small studies have reported longitudinal findings [3,4]; the majority of studies have been cross-sectional and their findings have been inconsistent [5-9].

We present a cross-sectional analysis of PFT among consecutive RA patients and a 5 year longitudinal follow-up study among patients agreeing to repeat evaluation and PFT. We report separately the PFT findings in the subgroup of the initial cohort that died during the study period. Variables related to changes in PFT measurements over 5 years were evaluated.

PATIENTS AND METHODS

CROSS-SECTIONAL ANALYSIS

The study population included consecutive patients with RA followed in the Rheumatology Clinic at Soroka Medical Center and fulfilling the American College of Rheumatology criteria for the classification of RA [10]. Patients were recruited for the study during the period 1 May 1998 to 31 January 1999. The duration of disease at the time of recruitment differed among patients. Patients were followed at 3–6 month intervals. Patients with prior pulmonary disease and known RA-related pulmonary involvement were excluded. A complete history, examination and laboratory evaluation were obtained and recorded on a standard retrieval protocol. All patients were treated with disease-modifying anti-rheumatic drugs at the time of enrollment in the study. Complaints and signs arising from the respiratory system, smoking status and other co-morbidities were also recorded. Comprehensive PFT was conducted.

FOLLOW-UP STUDY

Five years later all surviving patients were contacted to repeat the examination as above and those agreeing to participate comprised the follow-up study.

PULMONARY FUNCTION TESTING

All PFT were performed using the same equipment (Medgraphics, St Paul, MN, USA) in accordance with the recommendations of the American Thoracic Society [11,12]. One technician performed all PFT during 1998–99, but 5 years later PFT was done by two other technicians; all three technicians have vast experience in performing high quality PFT.

The variables measured were: forced vital capacity, forced expiratory flow in the first second, mid-expiratory flow, slow vital capacity, residual volume, total lung capacity, functional residual capacity, inspiratory capacity, diffusing capacity for carbon monoxide and pulse oximeter saturation. The variables are expressed as the mean of absolute values with standard deviation as well as percentage of the expected value corrected for gender, age and height according to the European Community for Steal and Coal, European Respiratory Society 1993. We also report the absolute yearly reduction in FEV1 and FVC.

FEV1 = forced expiratory volume in the first second
FVC = forced vital capacity

Table 1. Characteristics and co-morbidities of the rheumatoid arthritis patients at enrolment stratified according to participation at follow-up

	Returned	Lost to follow-up	Deceased
Number (%)	38 (46.3%)	29 (35.4%)	15 (18.3%)
Male:female	8:30	5:24	8:7
Mean age (yrs, SD)	53.4 (13.6)	53.8 (19)	65.9 (10.5)*
Ex-smokers	4 (10.5%)	3 (10.3%)	4 (26.7%)
Current smokers	6 (15.8%)	3 (10.3%)	1 (6.7%)
No co-morbidities	20 (52.6%)	15 (51.7%)	8 (53.3%)
Diabetes mellitus	3 (8%)	5 (17.2%)	1 (6.7%)
Hypertension	6 (16%)	9 (31%)	4 (26.7%)
Other*	3 (8%)	3 (10.3%)	6 (40%)
Rheumatoid arthritis duration (yrs, SD)	10.9 (9.5)	10.1 (10.9)	14.1 (10.4)

* Other: heart condition (n=6), dyslipidemia (n=2), peptic disease (n=2), lymphoma (n=1), hypothyroidism (n=1).
P = 0.002 (between deceased patients who were still alive)

Table 2. Laboratory variables and medical therapy of the RA patients on enrolment

	Returned (N=38)	Lost to follow-up (N=29)	Deceased (N=15)	*P*
ESR/1 hr (mm, mean)	45.6	30.8	30	0.42
Positive rheumatoid factor (%)	56.3%	52.6%	45.5%	0.00
Methotrexate (%)	71%	69%	66.7%	0.86
Prednisone (%)	58%	48.3%	60%	0.46
Gold (%)	29%	4.5%	9%	0.15
Anti-malarial (%)	56%	36.9%	0	0.002
Salazopyrin (%)	4.3%	28.6%	11.1%	0.008
Azathioprine (%)	17.2%	0	33%	0.2

ESR = erythrocyte sedimentation rate

DEFINITIONS OF DISTURBED PFT ACCORDING TO ATS GUIDELINES

Obstructive ventilatory defect – a disproportionate reduction of maximal airflow from the lung of the maximal volume displaced from the lung, and expressed as FEV1/ FVC ratio of less than 70%. The severity of the obstructive ventilatory defect is determined by the reduction in FEV1.

Small airways defect – a reduction in the mid-expiratory flow without reduction in FEV1/ FVC and expressed as reduced $FEF_{25–75\%}$.

Restrictive ventilatory defect – present when TLC is reduced (≤ 79 % of predicted) with a normal FEV1/FVC. When a restrictive ventilatory defect is associated with a reduction in CO diffusion capacity it is considered a disturbance that involves the lung parenchyma; if the DLco is not reduced it may be suggestive of conditions involving the thoracic cage, obesity or muscle weakness.

STATISTICAL ANALYSES

Statistical analyses were carried out using the STATA software. Descriptive statistics, chi-square test, and *t*-test were used to compare between patients. Linear analyses were conducted to identify variables associated with ≥ 20% change in PFT measurements (FEV1, FRC, TLC, RV, FVC, DLco)

RESULTS

Our cohort includes 82 patients with RA who underwent PFT; their mean age was 55.7 (SD 15.9) years and their mean RA duration was 11.1 (SD 10) years. Sixty-one (74%) were women and 21 (26%) were men.

Five years later our cohort of patients was stratified into three groups: the surviving 38 patients (46%) who returned for longitudinal follow-up study, 29 patients (35%) who were contacted and were alive but refused to repeat PFT and were defined as lost to follow-up, and 15 who died (18%). The demographics of the patients in the three groups, their smoking status and other co-morbidities are summarized in Table 1. The mean (SD) ages of the patients who died and those still alive were 65.9 years (10.5) and 53.4 (16.1) respectively. This difference was statistically significant ($P = 0.002$). Eight (53%) of the deceased patients were men and they constituted 38% of all of the males included in the study.

Laboratory data and medical therapy given to the patients for RA are shown in Table 2. Table 3 shows the PFD at enrollment.

$FEF_{25–75\%}$ = mid-expiratory flow
TLC = total lung capacity
FRC = functional residual capacity
RV = residual volume

THE CROSS-SECTIONAL STUDY

In the first PFT only 30 patients (36.6%) had normal PFT and 52 (63.4%) had abnormal findings. All patients were asymptomatic without any respiratory complaints at enrollment.

LONGITUDINAL STUDY

Five years after their first assessment 38 surviving patients (56.7%) were reevaluated and completed PFT, comprising the longitudinal follow-up study. Their demographics are shown in Table 1. Eight patients (21.1%) developed respiratory symptoms over the study period: five (6.1%) complained of shortness of breath and 3 (3.7%) complained of coughing.

DEFECTS FOUND ON PFT [Table 4]

- **An obstructive ventilatory defect** was found initially in two patients, one of whom was a current smoker and also had reduced DLco (consistent with a diagnosis of emphysema). Both patients were in the longitudinal group and showed a moderate obstructive ventilatory defect. Over the 5 year study period a third patient developed an obstructive ventilatory defect; this patient was a former smoker who initially had a small airways defect.
- **A restrictive ventilatory defect** was identified in 21 patients (25.6%); two belonged to the longitudinal follow-up group, 13 to the group lost to follow-up and 6 were deceased. The restrictive ventilatory defect was initially of mild severity in 16 (19.5%) and of moderate severity in 5 (6%). Medical therapy given to the patients for their restrictive defect during the duration of disease included methotrexate (all patients), prednisone (20 patients), and gold (10 patients). No correlation was found between restrictive defect and DLco values. During the 5 year study period one patient developed a new restrictive ventilatory defect.
- **A reduction in DLco** was initially seen in 17 patients (21%) – 8 in the longitudinal group, 5 in the group lost to follow-up, and 4 who were deceased. At the follow-up examination 5 years later the DLco had improved in seven of the eight patients who had had an initially reduced DLco, reaching normal values in five patients. However, in one patient, who was a smoker, further reduction in DLco was observed over the study period (consistent with emphysema). Seven patients had developed a new reduction in DLco. No association was found between reduction in DLco and the presence of restrictive ventilatory defect.
- **A small airways defect** was seen in 12 patients (14.6%): 6 patients were from the cohort of returning patients, 3 from the group lost to follow-up and 3 from among the deceased patients. Six (50%) of the patients with small airway disease were smokers. At follow-up five patients had a newly developed small airway defect, three of whom were not smokers. Of the two patients with an initial small airway defect, in one patient this reverted to normal PFT and, as mentioned above, one smoker progressed to a new obstructive ventilatory defect.

Table 3. Pulmonary function testing at enrollment, reported as percentage of expected values for age, gender and height

	Returned	Lost to follow-up	Deceased	*P*
Height (cm, SD)	159.9 (9.1)	158.1 (8.2)	158.9 (10.3)	0.69
Weight (kg, SD)	67.3 (16)	67.4 (14)	71.8 (18.6)	0.54
Forced vital capacity (% expected, SD)	77.1 (15.3)	74.6 (16.4)	63.3 (18.9)	0.02
Forced expiratory volume (% expected, SD)	83.1 (19.1)	80.4 (18.3)	69.3 (23.3)	0.08
FEV1/ FVC (%, SD)	88.1 (9.3)	90 (6.1)	86.5 (7.8)	0.34
Forced expiratory flow (% expected, SD)	98.6 (36.2)	98.8 (34)	82.9 (37.2)	0.33
Slow vital capacity (% expected, SD)	80.9 (14.4)	76.9 (14)	68.7 (18.9)	0.04
Inspiratory capacity (% expected, SD)	89.1 (19.5)	85.8 (22.3)	73.5 (22.5)	0.06
Functional residual capacity % expected (SD)	87.9 (21.5)	82.2 (17.4)	83 (22.8)	0.5
Residual volume (% expected, SD)	102.7 (31.7)	100.4 (41.8%)	94.7 (22.1)	0.75
Total lung capacity (% expected, SD)	88.5 (16.1)	83.8 (13.8)	78.3 (16.5)	0.17
DLco (% expected, SD)	86.1 (28.9)	94.7 (33.9)	94.7 (33.9)	0.798
O2 saturation (%, SD)	97.1 (0.8)	96.9 (1.4)	95.8 (1.7)	0.00

Table 4. Pulmonary abnormalities identified among patients with RA

Pulmonary abnormality	First assessment (N=82) (%)	No of cases in the returned group (first assessment) (N=38) (%)	Second assessment (N=38) (%)	New cases at second assessment (N=38) (%)
Obstructive ventilatory defect	2 (2.4)	2 (5.3)	3 (7.9)	1 (2.6)
Restrictive ventilatory defect	21 (25.6)	2 (5.3)	3 (7.9)	1 (2.6)
Small airways defect	12 (14.6)	6 (15.8)	10 (26.3)	5 (13.2)
Reduction in DLco	17 (20.7)	8 (21.1)	10 (26.3)	7 (18.4)

ABSOLUTE CHANGES IN PFT

Over the 5 year study period mean FEV1 decreased by 231 ml, i.e., a yearly decrease of 47 ml/year and FVC decreased by 188 ml, i.e., a yearly decrease of 38.2 ml/year. This was accompanied by a 199 ml increase in RV and a 296 ml increase in TLC.

Among the 38 patients who participated in the longitudinal study we found that 21 (55.3%) patients had a reduction in their height: 5 cm in 2 patients, 4 cm in 8 patients, 3 cm in 5 patients, and 2 cm in 6 patients. Among the 10 patients who lost 5 and 4 cm in height, all but 2 had been treated with steroid treatment.

LINEAR REGRESSION ANALYSES

Linear univariate analyses failed to identify any patient- or disease-specific characteristics that could predict a worsening in PFT (data not shown).

DISCUSSION

We performed PFT in 82 consecutive RA patients and found that the group of surviving patients had essentially normal PFT, while the group of patients who died during the study period had a mild restrictive ventilatory defect [Table 3]. To the best of our knowledge only two studies have reported on the longitudinal effect of RA on PFT with 8 and 10 year follow-up [3,4], and none of them reported PFT for patients with RA who died during the study period.

The most common PFT disturbance in our study was a small airways defect at initial evaluation in 12 patients (14.6%), 5 of whom were non-smokers. The $FEF_{25-75\%}$ reverted to normal in one non-smoker; while the small airway defect remained unchanged among the others, smokers and non-smokers alike. Over the 5 year period a new small airways defect developed in five patients, three of whom were non-smokers. A small airways defect is considered an early side effect of smoking.

The diagnosis of small airways abnormalities was based only on $FEF_{25-75\%}$. However, it is important to emphasize that $FEF_{25-75\%}$ is a highly variable spirometric test, in part because it depends on FVC. We did not perform computed tomography of the chest to confirm the diagnosis of small airway disease.

Three cross-sectional studies in RA patients also reported a high incidence of small airways defect expressed by a reduction of $FEF_{25-75\%}$ [5,6]. One group associated this with finding bronchiectasis in high resolution CT of the chest [6]. Our patients were asymptomatic and no crackles were found on auscultation; we therefore believe it unlikely that our patients suffered from significant bronchiectasis. Radoux et al. [13] found a small airway limitation in 50% of RA patients and concluded that this was associated with higher levels of antinuclear antibody. They also found HLA-DR4 in 80% of these patients, suggesting that small airway disease was an autoimmune exocrinopathy. It might be speculated that since today more effective DMARDs against RA might influence also this aspect of the disease, we found small airflow limitation in 14.6% and not in 50%. In addition, a different genetic background and change in the pattern of RA may be associated with a relatively lower rate of small airway diseases compared with studies conducted in the 1980s.

An earlier Danish longitudinal study of 63 RA patients reported initially a reduced transfer factor that reverted to normal after 8 years of follow-up [3]. Among our patients eight initially had a reduced DLco, but over the study period reached normal values in five patients and improved in two; further decline was seen in one smoking patient, suggesting emphysema. This finding was not reported by Fuld et al. [4]. The cause of a transient impairment in DLco among RA patients remains unknown; conditions that might explain a reduced DLco that improves over time could be, for example, anemia or congestive heart failure – neither of which was present in our patients at the time of their evaluation.

Five studies have reported serial follow-up of the influence of methotrexate on PFT in a total of 361 RA patients followed over a mean period of 23 months to 5 years [14-18]. All five studies concluded that serial PFT among patients with RA receiving methotrexate therapy is not a sensitive way to identify patients who may develop pulmonary toxicity. However, they did, encouragingly, conclude that disturbed PFT initially is not associated with an increased risk for developing methotrexate pulmonary toxicity [15-17].

Among 31 RA patients treated with methotrexate and followed for over 5 years a small but significant increase (5.1%) in RV was observed [17]. We also noted an absolute increase in RV of 0.530 L over the study period: the mean RV has increased from 102.7% of the predicted value at enrollment to 112.1% at the second assessment. This may be explained by the development of small airways obstruction among our patients. Linear regression analyses failed to identify any patient- or disease-specific characteristics associated with the increment in RV or other worsening in PFT.

Others found a predominantly restrictive ventilatory defect in patients with RA [7-9]; in our patients this was the second most common abnormality, detected in 15% of the patients at enrollment. However, in our longitudinal study only two patients had this disturbance – a finding difficult to explain.

Fifteen (18.3%) of our patients died over the 5 year period: the majority were men and compared to the surviving patients they were older with longer disease duration [Table 1]. Survival in RA has been reported to be related to RA disease activity and severity as well as associated cardiovascular conditions [18-20]; recently, methotrexate was associated with a survival benefit [21]. We observed a significantly reduced FVC, slow vital capacity and O_2 saturation among the deceased patients, suggesting that restrictive ventilatory defect is associated with increased mortality. In the general population reduced FVC and FEV1 as well as reduction in DLco have been correlated to reduced survival [22-24].

The predicted values of PFT are affected by various variables, including gender, age and height. We also noted a reduction of 1.82 cm in the height of the RA patients. This reduction in height may be the result of accelerated osteoporosis and vertebral compression, but we do not have data on this in our cohort.

DMARD = disease-modifying antirheumatic drugs

Among our patients, the mean change in FEV1 was 47 ml/year. It has been reported that non-smoking adults have a decrease in FEV1 of 20 ml/year and persons with considerable current smoking have a decrease of 45 ml/year [25]: only 25% of our group of patients were current or ex-smokers, indicating that other variables contributed to the accelerated decline in FEV1. A 2 year follow-up study of 55 patients with newly diagnosed RA treated with methotrexate reported an even larger decline than that seen among our patients: 92.1 ml/year [16]. These findings should lead to vigorously encouraging RA patients to refrain from smoking.

In agreement with Fuld and co-workers [4], who reported a high incidence of abnormal PFT among RA patients, our logistic regression analysis also failed to identify any patient- or disease-specific characteristics that could predict a worsening in PFT; also none of the treatment regimes correlated to worsening or improving PFT.

In summary, these data suggest that serial PFT among patients with RA identifies silent clinically relevant conditions that require follow-up and perhaps even intervention. Small airways disease is common in RA and needs to be further investigated.

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"There is only one difference between a madman and me. The madman thinks he is sane. I know I am mad"

Salvador Dali (1904-1989), Spanish surrealist painter, sculptor and photographer. Inspired by Freudian theories of the unconscious, he painted startling dream images with photographic realism during self-induced hallucinatory states. His eccentric behavior and self-advertisement earned him much criticism.