

Small airway obstruction in patients with rheumatoid arthritis

Shunsuke Mori · Yukinori Koga · Mineharu Sugimoto

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Abstract This work was intended to evaluate the prevalence of obstructive small-airway disease in patients with rheumatoid arthritis (RA) and its association with clinical characteristics. Pulmonary function testing (PFT) and high-resolution computed tomography (HRCT) were performed on 189 consecutive RA patients. Each case was diagnosed based on abnormal HRCT findings. We defined obstructive dysfunction of small airways as a forced expiratory flow from 25% to 75% of vital capacity (FEF_{25–75}) value >1.96 residual standard deviation (RSD) below predicted values. We found 19 patients (10.1%) with an interstitial pneumonia (IP) pattern and 15 (7.9%) with a bronchiolitis pattern; the other 155 (82.0%) had no abnormal HRCT patterns. In patients with neither abnormal pattern, median values of percentage predicted for carbon monoxide diffusing capacity (DL_{CO}) and ratio of DL_{CO} to alveolar ventilation (DL_{CO}/VA) were within the normal range, but median FEF_{25–75}, forced expiratory flow at 25% of vital capacity (V₂₅), and V₂₅/height were <70% of predicted values. Forty-seven patients (30.3%) in this group had obstructive small-airway dysfunction. Multivariate logistic

regression analysis indicated that this type of abnormality is strongly associated with respiratory symptoms [odds ratio (OR) 5.18; 95% confidence interval (CI) 1.70–15.75; $p = 0.012$], smoking history (OR 2.78; 95% CI 1.10–6.99; $p = 0.03$), and disease duration >10 years (OR 2.86; 95% CI 1.27–6.48; $p = 0.012$). Parenchymal micronodules, bronchial-wall thickening, and bronchial dilatation on HRCT scans were also predictive factors for abnormal FEF_{25–75}, although these morphological changes were too limited for us to diagnose these patients with the bronchiolitis pattern. Obstructive dysfunction of small airways is apparently common among RA patients, even among those with neither the IP nor the bronchiolitis pattern on HRCT scans. Factors significantly associated with abnormal FEF_{25–75} are respiratory symptoms, smoking history, and RA duration.

Keywords Disease duration · High-resolution computed tomography · Pulmonary function test · Rheumatoid arthritis · Small-airway obstruction

S. Mori (✉)

Department of Rheumatology, Clinical Research Center for Rheumatic Disease, NHO Kumamoto Saishunsou National Hospital, 2659 Suya, Kohshi, Kumamoto 861-1196, Japan
e-mail: moris@saisyunsou1.hosp.go.jp

Y. Koga

Department of Radiology, Clinical Research Center for Rheumatic Disease, NHO Kumamoto Saishunsou National Hospital, Kumamoto, Japan

M. Sugimoto

Division of Respiratory Medicine, Department of Medicine, NHO Kumamoto Saishunsou National Hospital, Kumamoto, Japan

Introduction

Rheumatoid arthritis (RA) is traditionally considered a chronic disease in which inflammatory changes occur predominantly in the synovial joints, but the systemic nature of this disease has also been noted in clinical studies and daily practice. In recent cohort studies, nearly 40% of patients with RA suffered from some type of extra-articular manifestations [1–3]. Extra-articular manifestations can be detected in almost all organ systems as cutaneous, ocular, hematological, cardiovascular, and pulmonary lesions; among the most common of these are pulmonary infection and drug-induced lung disease. Meanwhile, there has been

renewed interest in pulmonary complications directly associated with RA [4]. Postmortem studies on Japanese patients with RA have shown that pulmonary involvement is the second most common cause of death, being directly responsible for 9.9–17.5% of all mortality [5, 6]. The figures reported for the prevalence and incidence of pulmonary involvement in RA vary widely depending on the criteria used to define the disease, the sensitivity of the clinical investigations employed, and the patient populations examined [7, 8].

The pulmonary manifestations associated with RA have been evaluated through histopathological, radiological, and functional approaches. As abnormal radiological patterns seen on high-resolution computed tomography (HRCT) scans accurately reflect the underlying histological patterns revealed through lung biopsy [9–11], we recently performed HRCT scans on 126 patients with early or long-standing RA [12]. By evaluating one or two predominant abnormalities in each patient's HRCT findings and observing the distribution and extent of all abnormalities in the lungs, we gave each patient an HRCT-based diagnosis, such as an interstitial pneumonia (IP) pattern or a bronchiolitis pattern. In that study, we noted that a variety of morphological changes appear on HRCT scans in a considerable proportion of RA patients, though these abnormalities were too few for us to categorize such cases as belonging to the IP or bronchiolitis pattern. It remained unclear whether such patients may have functional impairment of the lung and whether such abnormalities are related to RA.

In this study, we performed pulmonary function testing (PFT) and HRCT scanning on 189 consecutive RA patients. These were categorized according to their HRCT findings into the following three groups: patients with the IP pattern, patients with the bronchiolitis pattern, and patients who were not diagnosed with any abnormal HRCT pattern. The functional abnormalities and clinical characteristics of these groups were compared. In addition, the prevalence of obstructive dysfunction in small airways among RA patients without the IP or bronchiolitis pattern on HRCT scans was determined. Finally, predictive factors for the presence of such functional abnormalities were identified through multivariate logistic regression analysis.

Patients and methods

Patients

Study participants were 189 Japanese patients with RA who had visited our outpatient clinic between January and May 2009. Patients were excluded from this study if they had any of the following histories: (1) pulmonary diseases

precluding an accurate pulmonary evaluation; (2) other collagen-vascular/autoimmune diseases; (3) exposure to dust such as asbestos or silica; or (4) thoracic radiation for cancer therapy. Of the initial population ($n = 231$), 42 patients were excluded for meeting one of the above-mentioned criteria; specific reasons for exclusion were as follows: atypical mycobacterial disease ($n = 1$), chronic bronchitis ($n = 2$), emphysema ($n = 19$), Sjögren's syndrome ($n = 7$), pleural involvement ($n = 1$), asbestosis ($n = 1$), clinically evident bronchiectasis ($n = 2$), bronchial asthma ($n = 3$), and middle lobe syndrome ($n = 6$). All participants fulfilled the 1987 American College of Rheumatology (ACR) criteria for diagnosis of RA. The ethics committee of our hospital approved the study protocol, and informed consent was obtained from all patients.

HRCT scanning and evaluation

A Somatom Sensation 4D CT scanner (Siemens, Erlangen, Germany) was used in this study. Thin-section scans were obtained with 2-mm collimation at 10-mm intervals, extending from the lung apices to the diaphragm. Technical factors were 120 kV and 130 mA. Images were reconstructed with a high-spatial-frequency algorithm. HRCT examinations were performed with patients in the supine position, at the suspended end-inspiratory volume, with imaging times of 1 s. All images were obtained at window levels appropriate for the lung parenchyma settings (window width 1,300–1,500 HU; window level -750 to -650 HU), and mediastinum (window width 400 HU; window level 30–50 HU). Images were reviewed in random order and independently by two observers (YK and SM) who were blinded to the patients' clinical status and PFT results. In the event of a disagreement, the final decision was made by consensus. Abnormal HRCT findings were defined according to the criteria described in our previous report [12]. For each case, we examined one or two predominant HRCT findings as well as the distribution and extent of abnormal findings and determined the probable diagnosis related to these pulmonary abnormalities according to the criteria on HRCT patterns defined by Tanaka et al. [9].

Pulmonary function tests

PFTs were performed on RA patients with or without abnormal HRCT patterns using a standard protocol. Vital capacity (VC), forced vital capacity (FVC), residual volume (RV)/total lung capacity (TLC), forced expiratory volume in the first second (FEV_1), FEV_1/FVC ratio (a sensitive index of overall airway obstruction), and forced expiratory flow from 25% to 75% of VC (FEF_{25-75} , a specific index of small airway function) were measured using a rolling-seal type of

spirometer (Chestac 8800; Chest Inc., Tokyo, Japan), with participants in a seated position. Peak expiratory flow (PEF) and forced expiratory flow at 25%, 50%, and 75% of VC (V_{25} , V_{50} , and V_{75}) were also recorded. Diffusing capacity for carbon monoxide (DL_{CO}) and DL_{CO} /alveolar volume (VA), indices of restrictive interstitial disease, were evaluated by a single-breath method using the same equipment. All PFTs were administered by two technicians who have a great deal of experience in performing high-quality PFTs. Measured values were compared with normal predicted values based on age, gender, and height of the individual, using regression equations installed in the spirometer; the equation for RV/TLC was formulated by Grimby and Soderholm [13], that for FEF_{25-75} by Schmidt et al. [14], those for PEF and V_{75} by Cherniack and Raber [15], that for V_{25} /height (Ht) by Yamamoto and Mitsufuji [16], and those for DL_{CO} and DL_{CO}/VA by Burrows et al. [17]. These regression equations are widely used in Japan to calculate normal predicted values. Measured values for VC, FVC, FEV_1/FVC , V_{50} , and V_{25} were compared with normal values determined by regression equations based on data from a sample of the general Japanese population and officially approved by the Japanese Respiratory Society (JRS statement 2001, <http://www.jrs.or.jp/quicklink/gls/index.html>). Results are expressed as a ratio of measured to predicted values (% predicted) unless otherwise indicated. We defined a patient as having small-airway obstruction if that patient's measured FEF_{25-75} value was >1.96 residual standard deviation (RSD) below the predicted value. This threshold marks the lower 95% confidence limit in a normal distribution; thus, 2.5% of the population will lie outside the normal range at the lower end [18, 19].

Statistical analysis

In univariate analyses of categorical variables, levels of significance were determined by means of the chi-square test using 2×2 contingency tables. If cell values were <5 , Fisher's exact probability test was used. Continuous variables were assessed using the Mann–Whitney U test. Multivariate logistic regression analysis was used to evaluate correlations between PFT abnormalities (as response variables) and a set of predictor variables, including age, disease duration (>10 years), respiratory symptoms, smoking history, and presence of anticyclic citrullinated peptide antibodies (anti-CCP Abs). A backward stepwise selection procedure was used to select significant predictor variables. The strength of association between functional abnormalities and these predictors was estimated using odds ratios (OR) and 95% confidence intervals (CI). In addition, the receiver operating characteristic (ROC) curves and the corresponding area under the curve (AUC) were calculated to provide an index of validity of

multivariate logistic regression models. For the construction of ROC curves, the true positive (sensitivity) and false positive (1-specificity) rates were plotted as the y and x axes, respectively. For all tests, probability values (p values) <0.05 were considered to indicate statistical significance. All calculations were performed using either Excel Statistical Analysis 2008 (SSRI Co., Ltd., Tokyo, Japan) or PASW Statistics version 17 (SPSS Japan Inc., Tokyo, Japan).

Results

Baseline characteristics of RA patients with or without abnormal HRCT patterns

Of the 189 patients examined, 34 (18.0%) were diagnosed with the IP pattern ($n = 19$) or the bronchiolitis pattern ($n = 15$) of HRCT abnormalities. In the other 155 patients (82.0%), the distribution and extent of abnormal HRCT findings were insufficient to warrant a diagnosis of abnormal HRCT patterns. As shown in Table 1, the patients in the IP group and those in the bronchiolitis group were more likely to complain of respiratory symptoms at the time of enrollment than were those without abnormal HRCT patterns ($p = 0.002$ and 0.000 , respectively). C-reactive protein (CRP) levels and erythrocyte sedimentation rates (ESR) were significantly higher in these two patient groups (CRP, $p = 0.042$ and 0.004 , respectively; ESR, $p = 0.002$ and 0.005 , respectively). The median age of both groups was significantly older than that of patients without abnormal HRCT patterns ($p = 0.0002$ and 0.031 , respectively). In addition, disease duration of patients with the bronchiolitis pattern was significantly longer than that of patients without abnormal HRCT patterns ($p = 0.037$); in none of the bronchiolitis-pattern patients was it <2 years. The patients in this group were more likely to suffer from severe joint damage, though this tendency did not reach statistical significance ($p = 0.055$). Parenchymal micronodules and bronchial-wall thickening, both of which are indicative of small-airway diseases, were more prominent in the bronchiolitis group ($p = 0.000$). Likewise, the frequency of bronchial dilatation was significantly higher in this patient population ($p = 0.004$).

PFTs of RA patients with or without abnormal HRCT patterns

The characteristic defects seen in PFTs of patients with the bronchiolitis pattern are those considered to indicate airway obstruction; obstructive defects in small airways were particularly prominent, as shown by decreases in FEF_{25-75} , V_{50} -Jpn, V_{25} -Jpn, and V_{25}/Ht to less than 50% of their

Table 1 Clinical characteristics of rheumatoid arthritis (RA) patients with or without abnormal high-resolution computed tomography (HRCT) patterns

	No abnormal pattern (<i>n</i> = 155)	IP pattern (<i>n</i> = 19 ^a)	<i>P</i> value*	Bronchiolitis pattern (<i>n</i> = 15)	<i>P</i> value*
Male/female	25/130	6/13	0.097	0/15	0.13
Age, years, median (25th, 75th percentiles)	60.0 (52.0, 70.0)	72.0 (68.0, 76.0)	0.0002	63.0 (59.0, 75.0)	0.031
Disease duration, years, median (25th, 75th percentiles)	4.0 (2.0, 9.0)	7.0 (3.0, 14.0)	0.45	7.0 (4.0, 13.0)	0.037
<2 years, numbers of patients (%)	42 (27.1)	3 (15.8)	0.41	0	0.024
>10 years, numbers of patients (%)	38 (24.5)	6 (31.6)	0.50	5 (33.3)	0.45
Steinbroker stage (III and IV), numbers of patients (%)	69 (44.6)	10 (52.6)	0.50	11 (73.4)	0.055
Respiratory symptoms, number of patients (%)	17 (11.0)	7 (36.8)	0.002	12 (80)	0.000
Current or former smokers ^b , numbers of patients (%)	27 (17.4)	5 (26.3)	0.34	2 (13.3)	1.00
Positive anti-CCP Abs	139 (89.7)	18 (94.7)	0.70	11 (73.3)	0.081
Positive RF	136 (87.7)	19 (100)	0.23	12 (80)	0.42
CRP, mg/dl, median (25th, 75th percentiles)	0.2 (0.06, 0.7)	0.3 (0.2, 1.1)	0.042	0.8 (0.3, 2.1)	0.004
ESR, mm/h, median (25th, 75th percentiles)	23.0 (14.0, 40.0)	39.0 (27.0, 59.0)	0.002	38.0 (32.0, 55.0)	0.005
Abnormal HRCT findings, numbers of patients (%)					
Parenchymal micronodules	25 (16.1)	1 (5.3)	0.31	14 (93.3)	0.000
Bronchial wall thickening	12 (7.7)	0	0.37	11 (73.3)	0.000
Bronchial dilatation	47 (30.3)	4 (21.1)	0.40	10 (66.7)	0.004

IP interstitial pneumonia, *anti-CCP Abs* anticyclic citrullinated peptide antibodies, *RF* rheumatoid factor, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate

* *p* values are based on comparison with patients without any abnormal HRCT patterns

^a One case may be considered to exhibit a mixed HRCT pattern, because the patient's HRCT revealed ground-glass attenuation, reticulation, and parenchymal micronodules as the predominant abnormalities. Nevertheless, we finally reached a consensus that the most predominant HRCT finding was ground-glass attenuation

^b ≥ 10 pack-years; one pack-year is defined as 20 manufactured cigarettes (1 pack) smoked per day for 1 year

predicted values (Table 2). In patients diagnosed with the IP pattern, the median % predicted values for DL_{CO} and DL_{CO}/VA , indices of restrictive changes, were significantly decreased. In the patient group with no abnormal pattern, median values of FEV_1/FVC and % predicted for DL_{CO} and DL_{CO}/VA were within the normal range. It is worth noting that the median % predicted values for FEF_{25-75} , V_{25-Jpn} , and V_{25}/Ht were markedly reduced (less than 70% of predicted values) in this patient group. These data show that obstructive changes in small, distal airways are present even in RA patients who have not been diagnosed with the bronchiolitis pattern seen on HRCT scans.

Correlation between clinical characteristics and PFT findings in RA patients without abnormal HRCT patterns

When we defined abnormal FEF_{25-75} as an FEF_{25-75} value >1.64 RSD below the predicted values, 13 patients (86.7%) in the bronchiolitis group (*n* = 15) and four (21.1%) in the IP group (*n* = 19) were diagnosed with obstructive dysfunction in small airways. When we defined abnormal FEF_{25-75} as an FEF_{25-75} value >1.96 RSD below the predicted values, 11 patients (73.3%) in the former

group and three (15.8%) in the latter were diagnosed with obstructive dysfunction in small airways. Among the 155 patients with neither abnormal HRCT pattern, 64 (41.3%) and 47 (30.3%) patients had FEF_{25-75} values >1.64 RSD and >1.96 RSD below predicted values, respectively (Table 3). Thus, obstructive dysfunction of small airways appears to be common in RA patients, including those without the IP or bronchiolitis HRCT pattern. In a comparison of patients in this group with measured FEF_{25-75} values >1.96 RSD below predicted values and the remainder of this patient group, low FEF_{25-75} values are more often seen in patients complaining of respiratory symptoms (OR 5.19; *p* = 0.001), those with smoking history (OR 2.57; *p* = 0.027), and those with disease duration >10 years (OR 2.35; *p* = 0.026). Bronchial/bronchiolar HRCT abnormalities such as parenchymal micronodules (OR 30.80; *p* = 0.000) and bronchial-wall thickening (OR 32.69; *p* = 0.000) were more frequently seen in patients with abnormal FEF_{25-75} (Table 3). The frequency of bronchial dilatation was also significantly higher in this group (OR 5.13; *p* = 0.0000), although these patients had not experienced clinically evident bronchiectasis. There was no significant difference in proportions of current steroid users between patients with abnormal FEF_{25-75}

Table 2 Pulmonary function tests of rheumatoid arthritis (RA) patients with or without abnormal high-resolution computed tomography (HRCT) patterns

	No abnormal patterns % predicted (<i>n</i> = 155)	IP pattern % predicted (<i>n</i> = 19)	Bronchiolitis pattern % predicted (<i>n</i> = 19)
VC-Jpn	101.8 (90.3, 112.0)	98.0 (86.2, 108.2)	85.4 (77.5, 107.6)*
FVC-Jpn	107.6 (94.8, 117.6)	100.5 (86.9, 115.0)	87.7 (82.6, 113.8)*
RV/TLC	109.6 (99.1, 122)	107.1 (96.5, 125.6)	122.0 (115.4, 129.7)**
FEV ₁ /FVC ^a	79.0 (74.3, 83.3)	82.3 (76.4, 87.3)*	72.0 (63.5, 77.4)***
FEV ₁ -Jpn	101.2 (90.5, 115.1)	102.3 (90.9, 118.2)	83.0 (69.2, 101.1)***
FEF _{25–75}	65.7 (49.0, 86.9)	82.6 (57.9, 110.9)*	38.1 (22.5, 56.1)***
PEF	72.4 (63, 81.4)	71.6 (61.5, 83.1)	53.4 (49.3, 67.8)***
V ₇₅	90.2 (76.6, 100.4)	89.5 (71.0, 97.4)	58.9 (41.2, 73.7)***
V ₅₀ -Jpn	78.8 (59.1, 104.2)	92.7 (67.0, 140.3)*	47.2 (30.8, 51.7)***
V ₂₅ -Jpn	52.8 (37.8, 71.8)	69.2 (39.8, 125.3)*	29.2 (25.3, 48.2)***
V ₂₅ /Ht	36.5 (27.6, 55)	47.9 (32.2, 72.8)	19.6 (12.5, 27.7)***
DL _{CO}	103 (91.5, 116.5)	82.3 (72.6, 97.0)***	96.3 (72.3, 113.7)
DL _{CO} /VA	82.3 (72.6, 93.7)	71.8 (57.4, 80.6)**	76.7 (71.6, 87.3)

Data are expressed as median (25th, 75th percentiles)

IP interstitial pneumonia, Jpn the Japanese reference population, VC vital capacity, FVC forced vital capacity, RV residual volume, TLC total lung capacity, FEV₁ forced expiratory volume in one second, FEF_{25–75} forced expiratory flow from 25 to 75% of VC, PEF peak expiratory flow, V₂₅, V₅₀, and V₇₅ forced expiratory flow at 25, 50, and 75% of VC, Ht height, DL_{CO} diffusing capacity for carbon monoxide, VA alveolar volume

* $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$ compared with patients without the abnormal HRCT patterns

^a Data are actual values, not % predicted

(nine out of 47, 19.1%) and those without this abnormality (13 out of 108, 12.0%).

Multivariate logistic regression analysis with a backward stepwise selection procedure confirmed that the presence of respiratory symptoms (OR 5.18, $p = 0.012$), smoking history (OR 2.78; $p = 0.03$), and disease duration >10 years (OR 2.86; $p = 0.012$) are significant factors independently associated with obstructive changes in small airways of RA patients who have neither IP nor bronchiolitis HRCT pattern (Table 4). The ROC curve showed that the final prediction model was moderately accurate (AUC, 0.71; 95% CI, 0.62–0.80; $p = 0.000$).

Discussion

Rheumatoid arthritis is known to cause upper- and lower-airway disease. The presence of functional and/or morphological abnormalities in small airways has recently been noted in RA patients, but the prevalence and clinical significance of bronchiolar disease is still a subject of debate [20]. The reported prevalence of obstructive dysfunction in small airways in RA patients, estimated on the basis of decreases in FEF_{25–75} values, varies among studies, ranging from 8% to 65% (Table 5). This variation may be explained by the different criteria used in different studies to assess small-airway disease as well as by variation in the

patient populations examined. Some studies performed PFTs only on RA patients without pulmonary symptoms or with normal chest radiographs [21–23]; others included unselected RA patients [24–31]. Percentages of patients with cigarette exposure also vary among studies, ranging from 14.6% to 76.7%. To define FEF_{25–75} abnormality, some investigators used the lower 90% or 95% confidence limit (i.e., 1.64 RSD or 1.96 RSD below the predicted values) [22, 26–28, 31], whereas others used fixed percentages of predicted values [21, 24, 25, 29, 30]. The participants in this study had no abnormal HRCT patterns, and 17.4% were former or current smokers. Seventeen (11.0%) complained of respiratory symptoms. We defined small airway dysfunction using the lower 95% confidence limit for FEF_{25–75} (< -1.96 RSD), which was determined by the regression equation of Schmidt et al. [14]. We concluded that under these conditions, the prevalence of obstructive small-airway disease in RA patients without the IP or bronchiolitis HRCT pattern is 30.3%. Application of the regression equation derived from the data of Quanjer et al. [18] decreased the prevalence of small-airway obstruction in this patient group somewhat, but the prevalence was still relatively high (Table 5). Normal values predicted for particular ages, genders, and heights may vary among different ethnic groups; unfortunately, no regression equation for FEF_{25–75} based on a Japanese reference population is available.

Table 3 Association of small-airway dysfunction with clinical and radiological characteristics in rheumatoid arthritis (RA) patients without abnormal high-resolution computed tomography (HRCT) patterns

	FEF ₂₅₋₇₅		P	FEF ₂₅₋₇₅		P
	<-1.64 RSD (n = 64)	≥-1.64 RSD (n = 91)		<-1.96 RSD (n = 47)	≥-1.96 RSD (n = 108)	
Female	53 (82.8)	77 (84.6)	0.76	38 (80.9)	92 (85.2)	0.50
Age, years, median (25th, 75th percentiles)	61.5 (54.0, 67.8)	59 (52.0, 70.0)	0.58	62.0 (56.0, 69.0)	59.0 (52.0, 70.0)	0.39
Disease duration, years, median (25th, 75th percentiles)	4.0 (2.0, 10.8)	4.0 (3.0, 8.0)	0.41	5.0 (2.0, 11.0)	4.0 (3.0, 8.0)	0.37
<2 years, numbers of patients (%)	18 (28.1)	24 (26.4)	0.81	14 (29.8)	28 (25.9)	0.62
>10 years, numbers of patients (%)	20 (31.3)	18 (19.8)	0.10	17 (36.2)	21 (19.4)	0.026 ^a
Steinbroker stage (III and IV), numbers of patients (%)	29 (45.3)	40 (44.0)	0.87	22 (46.8)	47 (43.5)	0.70
Respiratory symptoms, numbers of patients (%)	13 (20.3)	4 (4.4)	0.003	11 (23.4)	6 (5.6)	0.001 ^b
Current or former smokers [§] , numbers of patients (%)	15 (23.4)	12 (13.2)	0.098	13 (27.7)	14 (13.0)	0.027 ^c
Positive anti-CCP Abs, numbers of patients (%)	55 (85.9)	84 (92.3)	0.20	40 (85.1)	99 (91.7)	0.22
Positive RF, numbers of patients (%)	55 (85.9)	81 (89.0)	0.57	41 (87.2)	95 (88.0)	0.90
CRP, mg/dl, median (25th, 75th percentiles)	0.3 (0.1, 0.8)	0.2 (0.05, 0.7)	0.14	0.3 (0.1, 0.8)	0.2 (0.05, 0.7)	0.11
ESR, mm/h, median (25th, 75th percentiles)	28.0 (16.0, 44.0)	21.0 (14.0, 38.0)	0.06	26.0 (14.0, 40.0)	21.5 (14.3, 39.5)	0.48
Abnormal HRCT findings, numbers of patients (%)						
Parenchymal micronodules	22 (34.4)	3 (3.3)	0.0000	22 (46.8)	3 (2.8)	0.000 ^d
Bronchial wall thickening	11 (17.2)	1 (1.1)	0.0003	11 (23.4)	1 (0.9)	0.000 ^e
Bronchial dilatation	29 (45.3)	18 (19.8)	0.0007	26 (55.3)	21 (19.4)	0.000 ^f

FEF₂₅₋₇₅ forced expiratory flow from 25% to 75% of vital capacity, RSD residual standard deviation, anti-CCP Abs anticyclic citrullinated peptide antibodies, RF rheumatoid factor, CRP C-reactive protein, ESR erythrocyte sedimentation rate

Odds ratios (95% confidence intervals) were 2.35 (1.10–5.03)^a, 5.19 (1.79–15.07)^b, 2.57 (1.10–6.01)^c, 30.80 (8.54–111.08)^d, 32.69 (4.08–262.14)^e, and 5.13 (2.43–10.82)^f, respectively

[§] ≥10 pack-years; one pack-year is defined as 20 manufactured cigarettes (1 pack) smoked per day for 1 year

Table 4 Predictive factors for functional impairment in small airways of rheumatoid arthritis (RA) patients without abnormal high-resolution computed tomography (HRCT) patterns

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
FEF ₂₅₋₇₅ <-1.96 RSD				
Respiratory symptoms	5.19 (1.79–15.07)	0.001	5.18 (1.70–15.75)	0.012
Smoking history (>10 pack-years)	2.57 (1.10–6.01)	0.027	2.78 (1.10–6.99)	0.030
Disease duration >10 years	2.35 (1.10–5.03)	0.026	2.86 (1.27–6.48)	0.012

In the multivariate logistic regression analysis, low FEF₂₅₋₇₅ (<-1.96 RSD) was used as the dependent variable. Age, disease duration (>10 years), respiratory symptoms, smoking history, and presence of anticyclic citrullinated peptide antibodies were entered as the predictor variables (independent variables). In the final step, a significant influence of respiratory symptoms, disease duration (>10 years), and smoking history was detected, yielding an area under the receiver operating characteristic curve of 0.71

OR odds ratio, 95% CI 95% confidence interval, RSD residual standard deviation, FEF₂₅₋₇₅ forced expiratory flow from 25% to 75% of vital capacity

The clinical significance of small-airway dysfunction in RA remains to be elucidated. In a 10-year follow-up study, Fuld et al. [32] showed that PFT abnormality is a common finding in nonsmoking, asymptomatic patients with RA and that its incidence does not increase over time. These data may suggest that obstructive changes in the small airway are simply benign findings, though FEF₂₅₋₇₅ data were available

for only a small subset of their patients. In contrast, Avnon et al. [23] showed that 13.2% of RA patients participating in a 5-year follow-up study recently developed small-airway defect, defined as reduced FEF₂₅₋₇₅. Vergnenegre et al. reported a significant correlation between abnormal FEF₂₅₋₇₅ and duration of articular disease in nonsmokers with RA [28]. Similarly, through both univariate and

Table 5 Prevalence of small-airway dysfunction among rheumatoid arthritis (RA) patients on basis of reduced forced expiratory flow from 25% to 75% of vital capacity (FEF_{25–75})

	No. of patients	Patient population	No. of current or former smokers (%)	Definition of abnormal FEF _{25–75}	No. of patients having small-airway disease (%)
Collins et al. [24]	43	Unselected	33 (76.7)	<80% of predicted	28 (65.1) (92.9% had smoking history)
Geddes et al. [21]	100	Normal chest X-rays	53 (53)	<40% of predicted	38 (38) [14 (29.8) in nonsmokers]
Mountz et al. [25]	26	Unselected	14 (53.8)	<65% of predicted	12 (46.2) [9 (64.3) in smokers]
Banks et al. [26]	270	Unselected	NA	<−2 RSD	31 (11.5) (87.1% had smoking history)
Cortet et al. [27]	68	Unselected	16 (23.5)	<−1.64 RSD (< the lower 90% confidence limit)	9 (13.2)
Vergnenegre et al. [28]	100	Unselected	19 (19)	<−1.64 RSD	18 (18) [14 (17.3) in nonsmokers]
Perez et al. [22]	50	Normal chest X-rays	11 (22)	<−1.64 RSD and/or phase III slope ^a > 2 SD	4 (8)
Zrour et al. [29]	75	Unselected	11 (14.6)	<80% of predicted	27 (36)
Chung et al. [30]	39	Unselected	NA	<40% of predicted	16 (41.0)
Kanat et al. [31]	54	Unselected	12 (22.2)	< the lower 95% confidence limit (<−1.96 RSD)	8 (14.8)
Avnon et al. [23]	82	No symptom or evidence of respiratory disease	21 (25.6)	Reduced FEF _{25–75}	12 (14.6)
This study	155	No HRCT-based diagnosis of lung disease	27 (17.4)	<−1.64 RSD (Schmidt) <−1.96 RSD (Schmidt) <−1.64 RSD (Quanjer) <−1.96 RSD (Quanjer)	64 (41.3) 47 (30.3) 38 (24.5) 22 (14.2)

FEF_{25–75} forced expiratory flow from 25% to 75% of vital capacity, NA not available, RSD residual standard deviation, HRCT high-resolution computed tomography

^a The slope of phase III was determined by single-breath nitrogen washout test

multivariate analyses, we found that longer disease duration (>10 years) is a strong predictor for the presence of small-airway dysfunction defined as abnormal FEF_{25–75} (Table 4). These findings may suggest that small-airway disease has a long-term clinical significance as a manifestation of RA. In its early stages, obstructive changes in small airways are subtle, which makes it difficult to definitively diagnose the bronchiolitis pattern in HRCT images. Among these cases, some subset may subsequently develop clinically evident and HRCT-confirmed bronchiolitis during the course of RA. Indeed, we previously reported that bronchiolar abnormalities on HRCT scans are associated with RA duration [12]. Long-term follow-up studies are required to determine whether obstructive dysfunction in small airways is a benign finding or a predictive factor for future development of bronchiolitis. In this study, we showed that the presence of respiratory symptoms is strongly associated with obstructive abnormalities of small airways (Table 4). Thus, PFTs are encouraged for RA patients who have respiratory symptoms

and disease durations >10 years, even if the distribution and extent of the HRCT abnormalities in their lungs are not yet sufficient to warrant a diagnosis of bronchiolitis.

The contribution of RA to small-airway disease is obscured by the influence of other risk factors, such as cigarette smoking. We have shown that in patients with neither IP nor bronchiolitis HRCT pattern, the frequency of obstructive changes in small airways was likely to depend, at least in part, on tobacco exposure (Table 4). As Table 5 shows, several studies have found significant differences in the rates of small-airway disease between cigarette smokers with RA and nonsmokers with RA [24–26]. Small-airway obstruction may be secondary to cigarette smoking rather than to RA per se. Nevertheless, the frequency of small-airway dysfunction is still high in nonsmokers with RA [21, 28]. Its incidence has ranged from 13.2% to 36% in studies on patients with relatively lower rates (14.6–25.6%) of smoking history [23, 27, 29, 31]. Based on open lung biopsies, Hakala et al. [33] have suggested that smoking

alone cannot explain the development of bronchiolar lesions in patients with connective tissue diseases such as RA. These findings appear to be explained by an additive effect of RA and cigarette smoking on small-airway function; smoking exposure may potentiate and exacerbate RA-associated development of small-airway disease.

Several studies have suggested that the reduction in FEF_{25-75} seen in RA patients may reflect restrictive changes due to RA-associated interstitial lung disease [24, 26]. Interstitial fibrosis of the peribronchiolar areas may cause obstruction instead of restriction. Begin et al. [34] reported on six nonsmokers with RA and airway limitations; open lung biopsies of these cases showed inflammatory reaction and fibrotic proliferation in the peribronchiolar tissues, leading to complete obliteration of many bronchioles. Elsewhere, a high prevalence (8%) of small airway involvement was seen in RA patients without radiographic evidence of interstitial lung disease [22]. In our study, likewise, no restrictive ventilator disturbance on PFT was evident in the patient group without the IP or bronchiolitis pattern (Table 2). Sjögren's syndrome, which is often associated with RA, has been noted to cause peribronchiolar lymphocytic inflammation, subclinically leading to obstructive small-airway abnormalities [34–36]. Whether the complication of Sjögren's syndrome is a major contributor to the development of small-airway disease in RA patients remains to be elucidated. Perez et al. [22] showed that the presence of secondary Sjögren's syndrome is not related to abnormal PFT findings. Patients who had a history of Sjögren's syndrome were excluded from our study, and no participants revealed any clinical evidence of developing secondary Sjögren's syndrome during the subsequent follow-up period.

Anti-RA drugs such as penicillamine and gold have been associated with obliterative bronchiolitis [7, 37, 38]. None of the patients in our study had been treated with penicillamine or gold, however. Among our patients without an IP or bronchiolitis HRCT pattern, 143 (92.3%) had received methotrexate (MTX) at low dosages (6–10 mg/week); therefore, we cannot exclude the possibility that MTX use may influence small-airway function during the disease course, although there is no evidence to suggest that MTX use at low doses is associated with small airway function in RA patients, and most studies have found only minor subclinical alterations in pulmonary function in RA patients who have been treated with MTX at low doses [7, 39]. In our studies, we have found no significant differences in the duration or cumulative dosage of MTX therapy between patients with small-airway obstruction and those without (data not shown).

The reason for the high incidence of small-airway obstruction in RA patients remains unclear. One of the most attractive explanations is that the obstructive changes are

due to frequent and recurrent infections in the small airways. Colonization of the small airways by pathogenic microorganisms has been reported in patients with clinically stable bronchiectasis [40, 41], and a number of HRCT studies have shown that bronchiectasis is common among RA patients [22, 42–45]. We have also reported that bronchial dilatation is the most frequent HRCT finding both in patients with early RA and in those with longstanding RA [12]. Furthermore, in the study reported here, the prevalence of bronchial dilatation on HRCT scans was significantly higher in patients with abnormal FEF_{25-75} values (Table 3). Cortet et al. [27] also reported that bronchiectasis is more frequently seen in RA patients with low FEF_{25-75} values. Taken together, the evidence indicates that RA patients may have an increased susceptibility to airway infections or a reduced ability to eradicate these infections. Chronic colonization, secondary persistent inflammation, and progressive lung injury may contribute to the frequent development of airway obstruction during the disease course. In addition to bronchiectasis, there are several RA-related factors that are likely to increase the incidence of repeated bronchiolar infections. For example, orally administered steroids predispose RA patients to lower respiratory tract infection [46, 47]. In our study, however, the rates of orally administered steroid therapy were similar between patients with small-airway obstruction and those without. As an alternative explanation, several studies have proposed that bronchi/bronchioles are one of the main targets of autoimmunity in RA patients. Bronchiolar inflammation may secondarily induce mucosal edema, which eventually leads to development of small-airway obstruction [48]. Such pulmonary lesions may create a favorable environment for persistent infections. It is uncertain whether microbial colonization may precede bronchiolar obstructive changes or not. Regardless of which came first, a vicious spiral of infections and obstructive changes in the small airways can develop in the lungs of RA patients.

We found that among patients without abnormal HRCT patterns, there is no significant association between the presence of small-airway obstruction and the levels of CRP and ESR at the time of enrollment (Table 3). Perez et al. [22] also reported no correlation between RA-related parameters and small-airway dysfunction, defined as abnormal FEF_{25-75} . However, we cannot entirely rule out the possibility of a relationship between RA activity and small-airway disease, because disease activity varies over time. Time-integrated values of disease activity markers more accurately reflect the cumulative effects of disease activity during the course of RA; therefore, serial measurements of disease activity, starting in the early stages of RA, are required to address this question. The relationship between joint damage and small-airway obstruction is an important issue. As Table 3 shows, there were no significant

difference between patients with abnormal FEF_{25-75} and those without in the rate of classification into Steinbrocker stage III or IV. However, more sensitive assessment of joint damage may be required for a comparison among patients in the group without abnormal HRCT patterns.

In conclusion, we obtained evidence suggesting that obstructive dysfunction of small airways is common among RA patients, even among those without a diagnosis of IP or bronchiolitis pattern of HRCT abnormalities. The presence of respiratory symptoms, positive smoking history, and disease duration >10 years were predictive factors for the presence of abnormal FEF_{25-75} . This type of functional abnormality was more often seen in patients with bronchial/bronchiolar abnormalities on HRCT scans, although the distribution and extent of these patients' HRCT abnormalities were too limited to warrant a diagnosis of the bronchiolitis pattern. Restrictive disturbance was not evident in this patient group. The precise characterization of obstructive changes in small airways that is enabled by both PFT and HRCT appears to be helpful in evaluating not only their long-term significance as pulmonary complications of RA but also their implication in RA pathogenesis.

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Conflict of interest None.

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