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Estimation using the impulse oscillation system in patients with pulmonary sarcoidosis

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Abstract. *Background:* Limitations in airflow are detected in some patients with sarcoidosis in association with a poor prognosis. The impulse oscillation system (IOS) is used to treat patients with obstructive lung disease, as it can sensitively detect increased airway resistance. *Objectives:* To investigate the characteristics of parameters obtained with IOS in patients with sarcoidosis. *Methods:* Forty-six pulmonary sarcoidosis patients at Chiba University Hospital and 20 healthy controls were enrolled. The subjects underwent IOS, pulmonary function testing and multidetector computed tomography. We evaluated the correlations between these indices in the pulmonary sarcoidosis patients and compared the pulmonary sarcoidosis patients with the healthy controls. *Results:* The ratio of V_{50}/V_{25}, percentage of wall area (WA%), resistance at 5 Hz (R5) and difference between the R5 and R20 (R5-R20) values of the patients with pulmonary sarcoidosis were significantly increased compared to those observed in the controls. Inverse weak correlations were observed between the R5-R20 values and the forced expiratory volume in one second (r = -0.56; p <0.001). The R5-R20 values were correlated with the V_{50}/V_{25} (r = 0.42; p < 0.005) and WA% (r = 0.43; p < 0.05) values. The WA% values were also significantly correlated with the V_{50}/V_{25} (r = 0.32; p < 0.05) and R5 (r = 0.33; p < 0.05) values. *Conclusions:* IOS parameters were found to be significantly correlated with pulmonary function parameters and the airway wall thickness in pulmonary sarcoidosis patients. IOS is considered to be useful for detecting early manifestations of airflow limitation in pulmonary sarcoidosis patients. *(Sarcoidosis Vasc Diffuse Lung Dis 2015; 32: 144-150)*

Key words: pulmonary sarcoidosis, impulse oscillation system, percentage of wall area (WA%), resistance at 5 Hz (R5), difference between the R5 and R20 (R5-R20)

Introduction

Sarcoidosis is a systemic granulomatous disease of undetermined etiology characterized by a variable clinical presentation and disease course. Although clinical granulomatous inflammation may occur within any organ system, more than 90% of sarcoidosis patients have lung disease (1). Sarcoidosis is an interstitial lung disease that frequently presents with restrictive physiologic dysfunction on pulmonary function tests. However, sarcoidosis also involves the airways (large and small), causing obstructive airway disease (2).

Forced oscillometry is an effort-independent technique used to evaluate airway resistance (3). Two components of respiratory impedance can be

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evaluated using forced oscillometry: total respiratory resistance and reactance (4). Resistance at a low frequency, 5 Hz (R5), indicates total airway resistance, while resistance at a high frequency, 20 Hz (R20), reflects central airway resistance. The difference between R5 and R20 (R5-R20) is considered to be an index of the small airways (5). The reactance at 5 Hz (X5) is thought to be reciprocally related to compliance (6, 7). Forced oscillometry is primarily used to treat patients with obstructive lung disease, as it can sensitively detect increased airway resistance (4, 8). However, the characteristic findings of forced oscillometry in patients with pulmonary sarcoidosis have not been fully demonstrated.

In the present study, in order to investigate the characteristics of parameters obtained with forced oscillometry in patients with sarcoidosis, we measured respiratory resistance and reactance using an impulse oscillation system (IOS) in control subjects and patients with pulmonary sarcoidosis. We also evaluated the relationships between the IOS measurements and the results of pulmonary function tests (PFTs) and percentage of wall area (WA%) on multi-detector row CT (MDCT).

Methods

This study was approved by the ethics committee of Chiba University, and written informed consent was obtained from each participant.

Subjects

The study subjects included 46 consecutive patients (15 males) diagnosed with pulmonary sarcoidosis and 20 normal volunteers (8 males) suspected of having respiratory illnesses who were found to be healthy. All subjects underwent IOS, PFTs and MDCT on the same day at Chiba University Hospital during the period from December 2012 through February 2014. The diagnosis of pulmonary sarcoidosis was confirmed using pulmonary specimens obtained from transbronchial lung biopsies in all cases. None of the patients were treated for sarcoidosis or received steroids. The exclusion criteria for the enrolled patients with sarcoidosis included the following: (1) lung cancer, (2) heart failure, (3) a past history of smoking, (4) self-reported asthma and/or (5) endoscopic luminal abnormalities, such as mucosal coarseness, pallor, flat yellow mucosal plaque, irregular mucosal thickening, ulceration or atrophic mucosa.

Sarcoidosis criteria

The diagnosis of sarcoidosis was made based on consistent clinicoradiological features and the results of BAL fluid analyses, according to the American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and Other Granulomatous Disorders (ATS/ERS/WASOG) guidelines (9, 10). The definitive diagnosis was established when the clinicoradiological findings were supported by histologic evidence of noncaseating epithelioid cell granulomas and the exclusion of other diseases capable of producing similar histologic or clinical features. Granulomas of known causes and local sarcoid reactions were excluded.

Forced oscillometry

IOS (Eric Jaeger, Hoechberg, Germany) was used to assess respiratory impedance. The measurements were obtained according to the ERS/ATS guidelines and repeated immediately before spirometry fifteen minutes after bronchodilator administration (11). The system was calibrated through a single volume of air (3 L/minute) at different flow rates using a reference device (0.2 kPa/L/s). The machine was also calibrated to the air temperature and pressure of the saturated gas. The impulse generator produced brief pressure pulses at intervals of 0.2 seconds. The mean resistance (R) values were calculated over a measurement period of 60 seconds at frequencies of 5 Hz (R5) and 20 Hz (R20). The R5-R20 values were also calculated. The reactance (X) values were measured at 5 Hz (X5).

During IOS, the patient sat upright with their head resting against the back of the chair. They used nose clips and were instructed to breathe quietly through a mouthpiece. In order to decrease the shunt compliance of the cheeks, an investigator stood behind the patient and supported the chin and both cheeks with their hands. The observations did not demonstrate any artifacts caused by coughing, breath holding, swallowing or vocalization.

PFTs

The PFTs were performed on the same day as the IOS and MDCT scans. At 15 minutes after inhaling a short-acting bronchodilator, the PFT was performed using a CHSTAC-8900 (Chest MI Corp, Tokyo, Japan) according to the American Thoracic Society and European Respiratory Society guidelines (12). The total lung volume and diffusion capacity were measured via helium dilution and the single-breath method, respectively. The FEV_1% predicted and percentage of diffusing capacity per liter of lung volume (%D_{LCO}/VA) were calculated according to the Japanese Respiratory Society guidelines (13). The V_{50} and V_{25} values were also obtained, since the ratio of V_{50}/V_{25} is an index of small airway obstruction at a low lung volume.

MDCT scanning

All patients underwent 64-MDCT (Aquillion ONE; Toshiba Medical, Tokyo, Japan) at full inspiration. The scanner was calibrated regularly with an air and water phantom in order to obtain reliable measurements. No patients were given contrast medium. The MDCT scan parameters were as follows: collimation, 0.5 mm; 120 kV; 200 mA (Automatic Exposure Control system); gantry rotation time, 0.5 seconds; beam pitch, 0.83. All images were reconstructed using standard reconstruction algorithms with a slice thickness of 0.5 mm and a reconstruction interval of 0.5 mm. The voxel size was 0.63 × 0.63 × 0.5 mm. The reconstruction images were transferred to a commercially available workstation (Raijin; Aze; Tokyo, Japan).

CT measurements of the airway luminal and wall area

First, in order to evaluate the regional distribution of bronchial wall thickening, three bilateral bronchi were visually evaluated by two pulmonologists: the apical bronchus of the upper lobe (B1), medial bronchus of the middle lobe (B5) and anterior basal bronchus of the lower lobe (B8).

The reconstruction images were transferred to a commercially available workstation (Aze, AZE Ltd., Tokyo, Japan), after which a three-dimensional bronchial pathway was automatically reconstructed from the transverse, sagittal and coronal images. The bronchial pathway was converted to a curved multiplane reconstruction of the bronchial long-axis, from which the bronchial short-axis image perpendicular to the long axis was derived. The short-axis image was used to automatically calculate the parameters using the full width at half maximum principle. The outline of the airway wall was manually corrected when the computer-generated outline was obviously out of contour. The fifth (sub-subsegmental) bronchial generation was identified, and the area of the bronchiolar lumen (Ai) and the outer area of the bronchiole (Ao) were measured. The WA% was calculated as 100 x (Ao-Ai)/Ao. The apical bronchus of the upper lobe (B1) was evaluated on the inspiratory images (14). The values were confirmed by two observers (T.S. and K.T.) who were blinded to all clinical information.

Statistical analysis

Correlations between the IOS parameters, PFT parameters and MDCT parameters were examined using a Spearman rank correlation analysis. The data are presented as the mean ± standard deviation. The IOS parameters were compared between the patients with sarcoidosis and the control subjects using the Mann–Whitney *U*-test. For all statistical analyses, the level of significance was set at a p value of < 0.05. All statistical analyses were performed using the JMP 10.0 software program (SAS Institute, Cary, NC).

Results

Patient characteristics

The general characteristics of the 46 patients with pulmonary sarcoidosis (stage 0/I/II/III/IV: 10/19/12/3/2) and 20 normal subjects are shown in Table 1. Thirty-one patients (67%) with pulmonary sarcoidosis were female, with a mean age of 56.3 years, mean FEV_1 of 2.40 L, mean percentage of vital capacity (%VC) of 85.3% and mean %D_{LCO}/VA of 101.1%. Six patients exhibited a ratio of FEV_1/FVC (FEV_1/FVC) under 70%, eight patients exhibited a %VC under 80% and one patient exhibited a %D_{LCO}/VA under 80%. The V_{50}/V_{25} values of the patients with pulmonary sarcoidosis were signif-

Table 1. Clinical characteristics of enrolled patients

	Sarcoidosis patients	Normal controls	*p* value
Number of subjects	46	20	
Sex (male/female)	15/31	8/12	
Age, years	56.3 ± 15.6	54.7 ± 18.0	0.972
Stage (0/I/II/III/IV) (	10/19/12/3/2)		
sACE, IU/L	20.8 ± 10.8	NA	
VC, L	3.05 ± 0.97	3.40 ± 1.14	0.168
%VC, %	96.6 ± 15.6	100.6 ± 8.25	0.222
FEV_1, L	2.40 ± 0.90	2.55 ± 0.69	0.223
FEV_1% predicted, %	96.0 ± 20.9	98.1 ± 12.9	0.670
V_{50}	2.78 ± 1.31	3.96 ± 1.56	0.002
V_{25}	0.85 ± 0.62	1.68 ± 1.08	<0.001
V_{50}/V_{25}	3.78 ± 1.01	2.67 ± 1.00	<0.001
RV, L	1.59 ± 0.37	1.86 ± 0.32	0.822
TLC, L	4.67 ± 1.13	4.82 ± 1.21	0.909
%RV/TLC, %	35.0 ± 4.02	33.1 ± 13.1	0.487
$\%D_{LCO}$, %	91.4 ± 12.5	96.8 ± 14.2	0.454
$\%D_{LCO}/V_A$, %	101.1 ± 21.2	97.1 ± 12.6	0.753
WA%, %	67.9 ± 13.6#	50.0 ± 8.82##	0.048

sACE = serum angiotensin-converting enzyme (Reference range: 8.3 - 21.4 IU/L). R5 = respiratory system resistance at 5Hz. R20 = respiratory system resistance at 20 Hz. VC = vital capacity. FEV_1 = forced expiratory volume in one second. TLC = total lung capacity. RV = residual volume. D_{LCO}/V_A = diffusing capacity per liter of lung volume. WA% = percentage of the wall area of right apical bronchus. NA means not available. Data are expressed as mean ±SD. #: Two cases are excluded to analyze due to the difficulty of identifying right B1 airway for parenchymal shadows. ##: MDCT were performed for twelve cases.

icantly increased compared to those of the normal subjects (p <0.001). Meanwhile, the V_{50} and V_{25} values of the patients with pulmonary sarcoidosis were significantly decreased compared to those of the normal subjects (p =0.002 and p <0.001, respectively).

MDCT findings

The CT scans showed bronchial abnormalities, such as bronchial thickening, in 30 patients visually (67%). There was no significant visual laterality in the thickness of the bronchial walls. Of the 30 patients with CT findings of bronchial abnormalities, 27 (90%) had thickened bronchial walls in B1, 22 (73%) had thickened bronchial walls in B5 and 17 (57%) had thickened bronchial walls in B8.

The mean WA% of the right B1 was 67.9±13.6%. The WA% values of the patients with pulmonary sarcoidosis were significantly increased compared to those observed in the normal subjects (p=0.048, respectively) (Table 1).

IOS parameters

The whole-breath IOS results in the patients with sarcoidosis and controls are shown in Table 2. The R5 and X5 values in the control group were significantly lower than those observed in the sarcoidosis group (p=0.018, and p <0.001, respectively). In contrast, the R5-R20 and Z5 values in the sarcoido-

Table 2. IOS parameters of study subjects

	Sarcoidosis patients	Normal controls	*p* value
Number of subjects	46	20	
R5, $cmH_2O/L/sec$	0.34 ± 0.12	0.27 ± 0.05	0.018
R20, $cmH_2O/L/sec$	0.28 ± 0.08	0.25 ± 0.05	0.123
R5-R20, $cmH_2O/L/sec$	0.06 ± 0.05	0.02 ± 0.01	<0.001
X5, $cmH_2O/L/sec$	-0.14 ± 0.05	-0.09 ± 0.04	<0.001
Z5, $cmH_2O/L/sec$	0.37 ± 0.11	0.25 ± 0.07	<0.001

R5 = respiratory system resistance at 5 Hz. R20 = respiratory system resistance at 20Hz. X5 = respiratory system reactance at 5Hz. Z5 = respiratory system impedance at 5Hz. Data are expressed as mean ± SD.

Table 3. Correlation coefficients between IOS parameters and pulmonary function parameters

	R5	R20	R5-R20	X5
%VC	NS	NS	NS	0.59**
FEV_1	-0.60**	NS	-0.56**	0.59**
FEV_1% predicted	-0.33*	NS	-0.30*	0.43**
V_{50}/V_{25}	0.43**	NS	0.42*	NS
%RV/TLC	NS	NS	NS	-0.37**
$\%D_{LCO}/V_A$	NS	NS	NS	NS

R5 = respiratory system resistance at 5Hz. R20 = respiratory system resistance at 20Hz. X5 = respiratory system reactance at 5Hz. VC = vital capacity. FEV_1 = forced expiratory volume in one second. RV = residual volume. TLC = total lung capacity. D_{LCO}/V_A = diffusing capacity per liter of lung volume. NS means no significant correlations between parameters. Spearman rank correlation coefficients: * p <0.05, ** p <0.01.

sis group were significantly higher than those observed in the normal control group (p <0.001, and p <0.001, respectively).

Relationships between the parameters of IOS, PFT and MDCT

Inverse weak correlations were observed between the R5-R20 values and FEV_1 (r = -0.56; p <0.001) and FEV_1% predicted (r = -0.30; p <0.05) values (Table 3). The R5-R20 values were correlated with the V_{50}/V_{25} (r = 0.42; p <0.005) and WA% (r = 0.43; p <0.05) values (Table 3) (Fig. 1). The WA% values were also significantly correlated with the V_{50}/V_{25} (r = 0.32; p <0.05) and R5 (r =0.33; p <0.05) values, although the correlations between the WA% values and the FEV_1% predicted or X5 values were not statistically significant (Fig. 1).

Discussion

This is the first study to focus on the usefulness of IOS in evaluating airflow limitation in patients with sarcoidosis. Although the most common pulmonary function abnormality is a restrictive pattern caused by pulmonary parenchymal disease, in many patients with long-standing parenchymal sarcoidosis, obstructive disease can be pronounced (15-18). A past study documented that small airway dysfunction is common in patients with early sarcoidosis in the absence of restrictive defects. It has also been re-

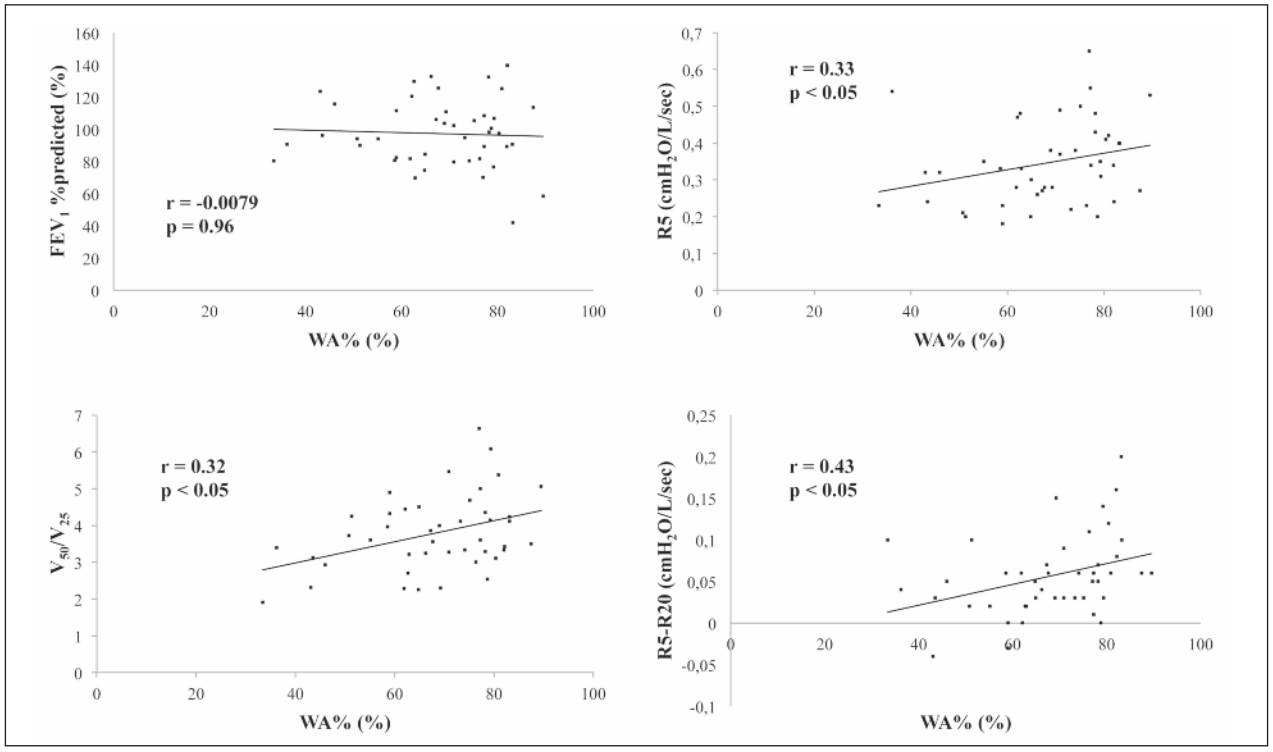

Fig. 2. Relationship between IOS parameters, PFT parameters, and MDCT parameters.WA% showed significant positive correlation with R5, R5-R20, and V_{50}/V_{25}.

ported that sarcoidosis patients with a FEV_1/FVC of <70% have an increased risk of mortality (odds ratio, 1.9) compared with those with a FEV_1/FVC of ≥70% (19). However, IOS parameters associated with airflow limitation in patients with sarcoidosis have not been fully elucidated.

In this study, we investigated IOS, PFT and radiographic indexes associated with airflow limitation in patients with sarcoidosis. We showed that the R5-R20 values, which are considered to be an index of the small airways, were higher in the patients with sarcoidosis than in the normal controls. We also observed the R5, R5-R20 and X5 values to be significantly associated with measurements of airway obstruction (FEV_1 and WA%) indicating that these IOS parameters represent the degree of airflow limitation and/or small airway involvement in sarcoidosis patients.

The pathogenesis underlying the deterioration of airflow in pulmonary sarcoidosis patients is not clear. Several factors have been considered, including airway narrowing due to granulomatous changes or fibrotic scarring in the central airways, peribronchiolar fibrosis, airway distortions caused by advanced parenchymal fibrosis, airway narrowing under the pressure of swollen lymph nodes, small airway disease and the accentuation of airway hyperreactivity (20). Peripheral bronchial granulomatous or fibrous changes are thought to be more important factors of airflow limitations, considering the report of a good response of obstructive disturbances to oral corticosteroid therapy in patients with pulmonary sarcoidosis in whom a peripheral bronchial biopsy revealed granulomatous changes (21).

The R5-R20 is thought to be an index of the small airways, and our R5-R20 results suggest the presence of small airway involvement in pulmonary sarcoidosis patients. The X5 is a measurement of reactance and is significantly associated with measurements of airway obstruction (FEV_1), hyperinflation (ratio of the residual volume to the total lung capacity) and restrictive impairment (VC) in patients with pulmonary sarcoidosis. Previous oscillometry studies have demonstrated that the same can be said of patients with chronic obstructive pulmonary disease (22-24). Our results also support the presence of peripheral bronchial changes in patients with pulmonary sarcoidosis, showing correlations between the WA% values and PFT or IOS parameters, such as V50/V25, R5 and R5-R20.

This study is associated with some limitations. The majority of our patients had relatively slight obstructive airway disturbances. This is because most Japanese patients with pulmonary sarcoidosis have slight interstitial lung disease and airflow limitation, as reported in a past study (25). This observation may also account for the absence of a correlation between the WA% and FEV_1% predicted. Additional studies are needed to assess more severe stages of pulmonary sarcoidosis. The present novel finding, however, is that even slight small airway obstruction in patients with pulmonary sarcoidosis can be detected sensitively using IOS.

Conclusions

In conclusion, IOS parameters reflect the pulmonary function and radiological findings in patients with pulmonary sarcoidosis. IOS is considered to be useful for evaluating airflow limitation in the setting of pulmonary sarcoidosis.

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