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Correlation between Computed Tomographic Analysis and Pulmonary Function Measurements in Patients with Relapsing Polychondritis

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Keywords
Computed tomography · Impulse oscillometry · Relapsing polychondritis · Spirometry · Tracheobronchial malacia

Abstract
Background: Relapsing polychondritis (RP) is a rare systemic disease of unknown origin, with cartilaginous involvement in multiple organs. Airway involvement is the most important prognostic factor in RP. ***Objectives:*** Spirometric measurements and minimum tracheal cross-sectional area (mtCSA) have been reported as useful to assess the degree of airway stenosis. Because the length and severity of tracheal involvement in RP can vary, mtCSA might not provide enough information to assess tracheal abnormalities. We introduced tracheal volume (TrV) as a new method to evaluate correlations between chest computed tomography (CT) measurements and pulmonary function tests, including impulse oscillometry (IOS). ***Method:*** We analyzed chest CT images, spirometry, and IOS collected at our institution from April 2004 to March 2019. We calculated correlations between chest CT measurements using software (TrV, TrV/tracheal length [TrV/TL], and mtCSA) and pulmonary function parameters. ***Results:*** Twenty-five of 73 clinically diagnosed patients with RP were included. Spirometric findings showed moderate airway obstruction. Peak flow (PEF) was strongly correlated with mtCSA, TrV, and TrV/TL ($\rho = 0.74$, $p < 0.001$). FEV1 was significantly correlated with mtCSA ($\rho = 0.56$, $p = 0.004$), TrV ($\rho = 0.52$, $p = 0.007$), and TrV/TL ($\rho = 0.53$, $p = 0.006$). Whereas respiratory resistance at 5 Hz (R5) and 20 Hz (R20) and resonant frequencies (RFs) were significantly correlated with TrV ($\rho = -0.46$, $p = 0.021$; $\rho = -0.46$, $p = 0.046$; and $\rho = -0.42$, $p = 0.037$, respectively), IOS parameters and mtCSA were not. ***Conclusions:*** In patients with RP, TrV and mtCSA were strongly correlated with spirometric measurements. Respiratory resistances assessed by IOS correlated only with TrV. This suggests TrV assessment reflects pulmonary function in patients with RP more appropriately than mtCSA.

Introduction

Relapsing polychondritis (RP) is a rare systemic disease of unknown origin, characterized by cartilaginous involvement of multiple organs. Patients are most commonly aged in their 40–50s at presentation. The male:female

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ratio has been reported to be 1:3 [1]. A Japanese survey conducted in 2009 reported the clinical course for 239 patients with RP and found that 72.3% of patients showed improvement, 13.3% were unchanged, 3.8% worsened, and 9.2% died [2]. Laryngo-tracheal disorders were the leading cause of death, found in approximately 10–50% of patients [3, 4]. As inflammation progresses, respiratory symptoms such as hoarseness, dry cough, and wheezing can occur. Airway inflammation causes airway cartilage destruction, resulting in airway stenosis and tracheobronchial malacia. Emergency tracheoplasty is often required to treat respiratory failure. Airway lesions are the most important prognostic factors, and the diagnosis and treatment for RP are influenced by these lesions.

We have previously studied the relationship between parameters derived from chest computed tomography (CT) assessment and pulmonary function [5, 6]. We reported that minimal tracheal cross-sectional area (mtCSA) likely determines the severity of airflow limitation in RP [5]. However, tracheal lesions can vary in length and severity in patients with RP [7]. Thus, it is possible that mtCSA might not provide enough information for the assessment of tracheal abnormality in RP.

Previously, the usefulness of evaluating tracheal volume (TrV) was reported for obstructive pulmonary diseases [8, 9]. Yamashiro et al. [8] reported that the ratio of inspiratory to expiratory TrV was correlated with spirometric measurements in smokers and patients with chronic obstructive pulmonary disease (COPD) [8]. In the present study, we introduced TrV and TrV/tracheal length (TL) to reflect the mean tracheal CSA as new tools for assessing tracheal involvement in patients with RP. Because some patients with RP are unable to undergo spirometry safely, we have applied impulse oscillometry (IOS) to evaluate pulmonary function in patients with RP and airway stenosis [10, 11]. IOS is an effort-independent pulmonary function test that is safe for the assessment of airway dysfunction in patients with RP who have severe airway obstruction. We evaluated the correlation between chest CT measurements (TrV, TrV/TL, and mtCSA) and pulmonary function tests (Spirometry and IOS parameters).

Materials and Methods

The Ethics Committee of St. Marianna University School of Medicine approved this retrospective study. The need for informed consent was waived.

Table 1. Characteristics of RP patients

	Mean, SD	Range
Age, years	53 (±15)	31–80
Sex (M/F)	12/13	
Height, cm	160.6 (±8.59)	139–177
Weight, kg	56.7 (±13.8)	28–100
Spirometry		
FEV1, L	1.49 (±0.72)	0.6–3.23
FEV1 (%)	52.7 (±20.2)	20.3–101.3
%FEV1 (%)	56.8 (±24.2)	24.0–101.3
FVC, L	2.86 (±0.81)	1.36–5.03
VC, L	2.94 (±0.80)	1.43–5.03
%VC (%)	89.2 (±14.1)	67.3–121.1
PEF, L/s	4.17 (±2.59)	1.41–10.56
FEF 50, L/s	1.31 (±1.11)	0.18–4.42
FEF 25, L/s	0.53 (±0.39)	0.18–1.56
IOS		
R5, kPa/[L/s]	0.50 (±0.29)	0.21–1.41
R20, kPa/[L/s]	0.34 (±0.10)	0.18–0.55
R5-R20, kPa/[L/s]	0.17 (±0.22)	−0.86 to −0.04
X5, kPa/[L/s]	−0.22 (±0.22)	−0.94 to −0.04
RF, 1/s	18.4 (±7.6)	8.7–33.3
CT measurements		
TrV, mL	18.5 (±8.2)	7.3–40.6
TrV/TL, mm^2	171.2 (±69.9)	80.0–336.8
mtCSA, mm^2	126.8 (±66.1)	41–273

FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s; FEF50, forced expiratory flow at 50% of the FVC; FEF25, FEF at 25% of FVC; PEF, peak flow; R5, respiratory resistance at 5 Hz; R20, respiratory resistance at 20 Hz; ΔR5, difference between the resistance at 5 Hz; R5-20 Hz, resistance at 20 Hz; X5, reactance at 5 Hz; RF, resonant frequency; TrV, tracheal volume; TrV/TL, TrV/tracheal length; mtCSA, minimal tracheal cross-sectional area; RP, relapsing polychondritis; CT, computed tomography.

Participants

We reviewed the medical records and previous chest CT images, spirometry, and IOS parameters at our institution from April 2004 to March 2019. We reviewed a total of 73 consecutive patients with RP who were clinically diagnosed according to the diagnostic criteria of McAdam et al. [12] and Damiani and Levine [13]. Patients were excluded if IOS was not performed (n = 28), they had previous stent placements (n = 10), thin-slice chest CT had not been performed within 4 weeks of IOS (n = 9), or if there were severe bronchial obstructive lesions (n = 1). Finally, 25 patients were included. The patients were stable without previous exacerbation at the time of their examination, which was held as either inpatient or outpatient. The patient characteristics are summarized in Table 1.

Pulmonary Function Tests

Spirometry (Fudac77; Fukuda Electronics, Tokyo, Japan) and IOS (MasterScreen IOS; CareFusion, San Diego, CA, USA) were performed according to ATS/ERS guidelines [14]. We evaluated the following spirometry parameters: forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), forced expiratory flow at

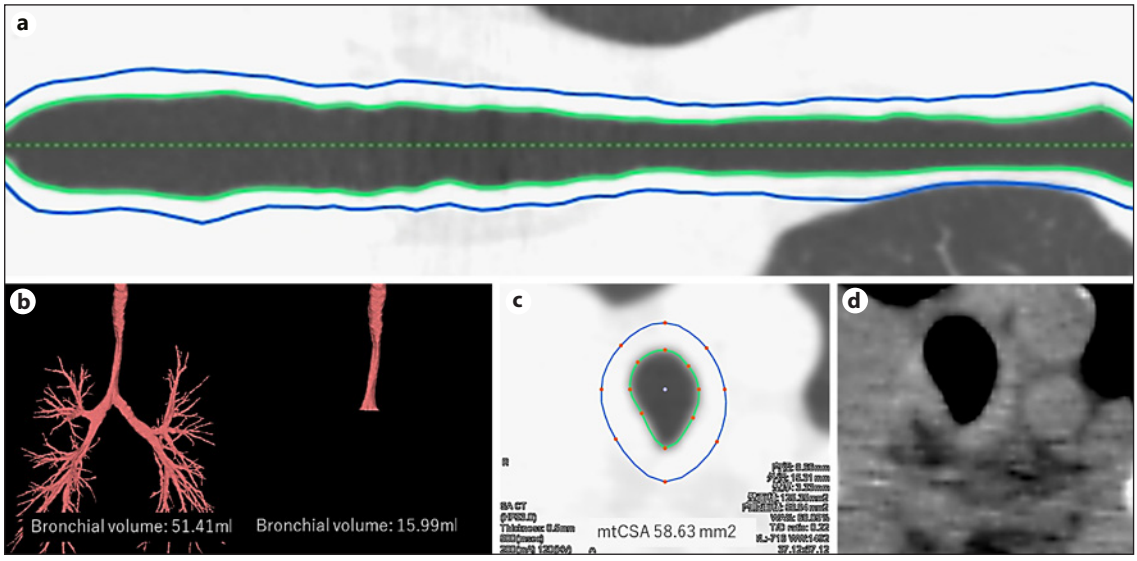

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Fig. 1. The Ziostation2 software automatically detected airway volume and showed the lumen of each 0.5 mm slice with the graph in about 5 min. **a**, **b** We manually deleted extra-tracheal air regions (the lungs and bronchi) on each image and defined the remaining part as TrV. **c** The mtCSA was detected by the graph on multi-planar reconstructed images. **d** An axial image of the soft tissue. mtCSA, minimum tracheal cross-sectional area.

50% of the FVC (FEF50) maneuvers, FEF at 25% of FVC (FEF25) maneuvers, and peak flow (PEF). IOS parameters were respiratory resistance at 5 Hz (R5), respiratory resistance at 20 Hz (R20), the difference between R5 and R20 (R5-20 Hz), reactance at 5 Hz (X5), and resonant frequency (RF).

Computed Tomography

Patients were scanned using a 64- or 80-row detector CT scanner (Aquilion 64 or Aquilion PRIME, respectively; Toshiba Medical Systems, Otawara, Japan). Chest CT was performed in the supine position during a breath hold at full inspiration. Patients were instructed how to hold their breaths before scanning by the performing technician. The scanning parameters for CT scans were as follows: collimation, 0.5 mm; tube voltage, 120 kV; gantry rotation time, 0.5 s; and beam pitch, 0.828 (Aquilion 64) or 0.813 (Aquilion PRIME). We used Ziostation2 (Ziosoft, Tokyo, Japan) to measure TrV, TL, and CSA at the narrowed site of the trachea.

Ziostation2 software automatically detected airway volume and displayed the lumen of each 0.5 mm slice with the graph in about 5 min. We manually deleted extra-tracheal air regions (the lungs and bronchi) on each image and defined the remaining part as TrV (shown in Fig. 1a–c). The mtCSA was measured using the graph (shown in Fig. 1d). TL was defined as the distance from the vocal cords to the carina by counting CT slices, and TrV/TL was calculated as TrV divided by TL (shown in Fig. 2).

Statistical Analysis

Results are expressed as means ± SD. All analyses were performed using JMP 9.0 software (SAS Institute, Cary, NC, USA). Correlations between pulmonary function tests (spirometry and IOS) and chest CT measurements were evaluated using Spearman correlation tests. Differences were considered significant when 2-tailed p values were <0.05.

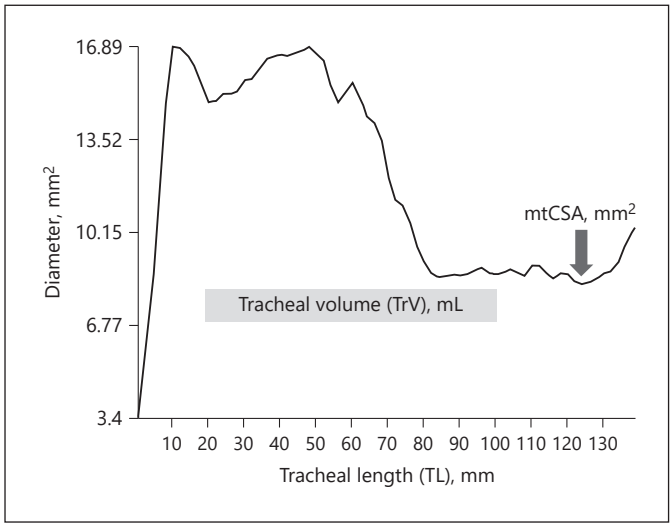

Fig. 2. Airway measurements using Ziostation2 software. mtCSA, minimum tracheal cross-sectional area; TrV, tracheal volume; TvL, tracheal length.

Results

The spirometric findings of 25 patients with RP showed moderate airway obstruction as follows: VC, 2.94 ± 0.80 L; %VC, 89.2 ± 14.1%; FEV1, 1.49 ± 0.72 L; and FEV1%, 52.7 ± 20.2%. Compared with the previous healthy Japanese participants [15], the IOS parameters revealed that

Table 2. Correlation between pulmonary function test and airway measurements in chest CT

	Chest CT measurements					
	TrV		TrV/TL		mtCSA	
	ρ	*p* value	ρ	*p* value	ρ	*p* value
Spirometry						
FEV1	0.52	0.007	0.53	0.006	0.56	0.004
FEV1 (%)	0.39	0.053	0.36	0.081	0.51	0.009
FEV1 (%)	0.39	0.053	0.37	0.067	0.52	0.008
FVC	0.35	0.089	0.4	0.05	0.23	0.267
VC	0.4	<0.05	0.45	0.024	0.26	0.208
VC (%)	0.22	0.5	0.22	0.289	0.1	0.62
PEF	0.74	<0.001	0.74	<0.001	0.74	<0.001
FEF 50	0.48	0.016	0.47	0.019	0.53	0.007
FEF 25	0.49	0.013	0.49	0.013	0.45	0.022
IOS						
R5	−0.46	0.021	−0.42	0.035	−0.22	0.286
R20	−0.4	0.046	−0.34	0.092	−0.28	0.175
R5-R20	−0.26	0.214	−0.26	0.212	−0.06	0.773
X5	0.35	0.082	0.33	0.107	0.14	0.51
RF	−0.42	0.037	−0.39	0.053	−0.2	0.345

FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s; FEF50, forced expiratory flow at 50% of the FVC; FEF25, FEF at 25% of FVC; PEF, peak flow; R5, respiratory resistance at 5 Hz; R20, respiratory resistance at 20 Hz; ΔR5, difference between the resistance at 5 Hz; R5-20 Hz, resistance at 20 Hz; X5, reactance at 5 Hz; RF, resonant frequency; TrV, tracheal volume; TrV/TL, TrV/tracheal length; mtCSA, minimal tracheal cross-sectional area; IOS, impulse oscillometry; CT, computed tomography.

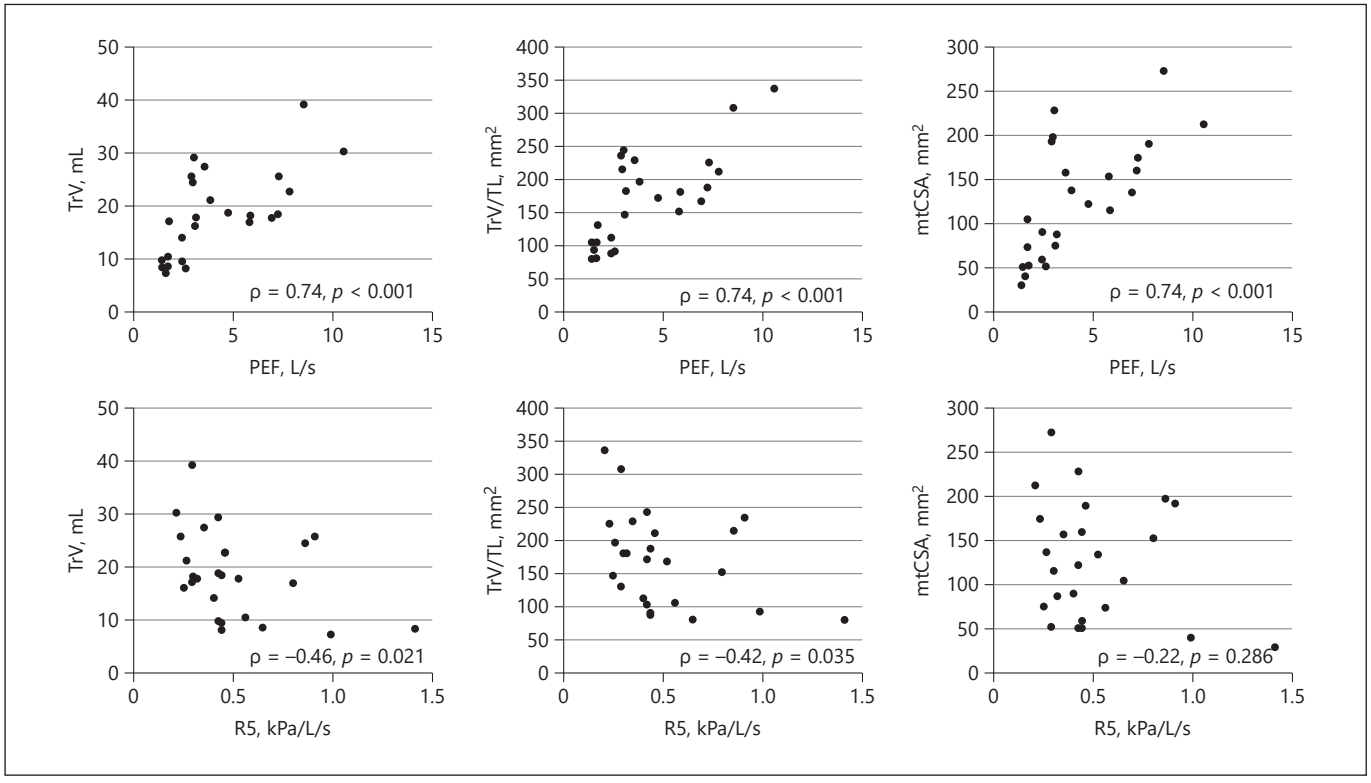

Fig. 3. Correlations between pulmonary function and CT measurements. CT, computed tomography; TrV, tracheal volume; TrV/TvL, TrV/tracheal length; PEF, peak flow; R5, respiratory resistance at 5 Hz; mtCSA, minimum tracheal cross-sectional area.

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Table 3. Correlation between spirometry and IOS parameters

N = 25 IOS	Spirometry					
	VC		%VC		FVC	
	ρ	*p* value	ρ	*p* value	ρ	*p* value
R5	−0.41	0.043	−0.44	0.028	−0.38	0.058
R20	−0.22	0.285	−0.1	0.648	−0.22	0.29
R5-R20	−0.57	0.003	−0.59	0.002	−0.56	0.004
X5	0.58	0.003	0.62	0.001	0.59	0.002
RF	−0.49	0.012	−0.63	<0.001	−0.49	0.014
	FEV1		FEV1%		%FEV1	
	ρ	*p* value	ρ	*p* value	ρ	*p* value
R5	−0.36	0.073	−0.22	0.321	−0.25	0.236
R20	−0.15	0.476	−0.12	0.571	−0.13	0.523
R5-R20	−0.43	0.034	−0.13	0.545	−0.2	0.339
X5	0.43	0.031	0.14	0.493	0.24	0.249
RF	−0.42	0.039	−0.18	0.393	−0.27	0.191
	PEF		FEF50		FEF25	
	ρ	*p* value	ρ	*p* value	ρ	*p* value
R5	−0.48	0.014	−0.28	0.17	−0.28	0.182
R20	−0.31	0.126	−0.01	0.578	−0.01	0.98
R5-R20	−0.43	0.033	−0.28	0.173	−0.32	0.119
X5	0.47	0.017	0.3	0.145	0.41	0.044
RF	−0.47	0.017	−0.33	0.102	−0.35	0.09

FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s; FEF50, forced expiratory flow at 50% of the FVC; FEF25, FEF at 25% of FVC; PEF, peak flow; R5, respiratory resistance at 5 Hz; R20, respiratory resistance at 20 Hz; ΔR5, difference between the resistance at 5 Hz; R5-20 Hz, resistance at 20 Hz; X5, reactance at 5 Hz; RF, resonant frequency; TrV, tracheal volume; TrV/TL, TrV/tracheal length; mtCSA, minimal tracheal cross-sectional area; IOS, impulse oscillometry.

R5, R20, and RF were higher (0.50 ± 0.29 kPa/L/s, 0.34 ± 0.10 kPa/L/s, and 18.4 ± 7.6 /L, respectively), and X5 was lower in patients with RP (−0.22 ± 0.22 kPa/L/s). The mean TrV and mtCSA were 18.5 ± 8.20 mL and 126.8 ± 66.1 mm^2, respectively (shown in Table 1).

As in our previous report [5], mtCSA was strongly correlated with spirometric parameters such as PEF (ρ = 0.74, $p < 0.001$) and FEV1 (ρ = 056, $p = 0.004$). However, there were no correlations between mtCSA and IOS parameters (shown in Table 2).

TrV and TrV/TL were strongly correlated with PEF (ρ = 0.74, $p < 0.001$ and ρ = 0.74, $p < 0.001$, respectively) and FEV1 (ρ = 0.52, $p = 0.007$ and ρ = 0.533, $p = 0.006$, respectively). TrV and TrV/TL were significantly correlated with IOS parameters (shown in Fig. 3). TrV was significantly correlated with R5, R20, and RF (ρ = −0.46, $p = 0.021$; ρ = −0.40, $p = 0.046$; and ρ = −0.42, $p = 0.037$, respectively). TrV/TL was also significantly correlated with R5 (ρ = −0.42 and $p = 0.035$) and tended to correlate with R20 and RF (ρ = −0.34, $p = 0.092$ and ρ = −0.39, $p = 0.053$, respectively) (shown in Table 2).

Compared to R5-R20, X5, and RF were more strongly correlated with VC and %VC (R5-R20: ρ = −0.57, $p = 0.003$ and ρ = −0.59, $p = 0.002$; X5: ρ = 0.58, $p = 0.003$ and ρ = 0.62, $p = 0.001$; and RF: ρ = −0.49 $p = 0.012$ and ρ = −0.63, $p < 0.001$). PEF was significantly correlated with IOS parameters without R20 (R5: ρ = −0.48, $p = 0.014$; R20: ρ = −0.31, $p = 0.126$; R5-R20: ρ = −0.43, $p = 0.033$; X5: ρ = 0.47, $p = 0.017$; and Fres: ρ = −0.47, $p = 0.017$). Significant correlations were only found between FEV1 and IOS parameters (R5-R20: ρ = −0.43, $p = 0.031$; X5: ρ = 0.43, $p = 0.031$; and Fres: ρ = −0.42, $p = 0.039$). No correlations between the other spirometric parameters and IOS parameters were noted. In addition, R20 was not significantly correlated with any of the spirometric parameters (shown in Table 3).

Discussion

To our knowledge, this is the first report to evaluate correlations between TrV and pulmonary function tests in patients with RP. In this study, TrV and TrV/TL were correlated with spirometric measurements as well as the mtCSA. While there were no correlations between mtCSA and IOS parameters, TrV and TrV/TL were significantly correlated with IOS parameters. We believe that TrV assessment reflects pulmonary function in patients with RP more appropriately than mtCSA.

We showed that mtCSA was correlated with PEF and FEV1, as in our previous report [5]. The condition of the central airway may be reflected by mtCSA. RP gives rise to several airway stenosis types, including subglottic stenosis, tracheal stenosis, and tracheobronchial malacia. The airway lesions of RP vary in their length and severity [7]. We hypothesized that mtCSA might not provide enough information to assess complicated tracheal abnormalities in RP. Yamashiro et al. [8] reported that the ratio of inspiratory to expiratory TrV is correlated with FEV1 and FVC in smokers. Camiciottoli et al. [9] also reported that intrathoracic tracheal collapsibility is correlated with inspiratory minus expiratory volume variation on CT and with FEV [9]. In the present study, we introduced TrV assessment for the evaluation of pulmonary function in patients with RP. Although we could only evaluate inspiratory TrV measurements, this method appeared to more precisely reflect pulmonary function than mtCSA in patients with RP.

Spirometry is the gold standard for pulmonary function tests for airway involvement in RP. In the early stage, the airway wall becomes thickened without airway narrowing, and spirometric values are within the normal range. As the disease progresses, the airway starts narrowing and dynamic airway collapse occurs, resulting in airflow limitation seen on flow-volume curves during inspiration and expiration [16]. However, spirometry is an effort-dependent maneuver. It is difficult and sometimes dangerous to perform spirometry for patients with severe airway obstruction.

IOS is a forced oscillation technique that does not require expiratory maneuvers [15, 17, 18], using a small loudspeaker to generate pressure pulses of 5–35 Hz. Previous studies have reported that IOS is equivalent to spirometry in patients with asthma and COPD [19–21]. In addition, IOS parameters can be used to determine stenosis type and severity of central airway obstruction [10]. Central airway stenosis is thought to exhibit increased R5 and R20, with minimal impact on reactance. R5 and R20 may be safe and useful in monitoring and assessing airway condition in patients with RP. In this study, mtCSA did not correlate with IOS parameters. IOS is an effort-independent pulmonary function test; therefore, mtCSA appears insufficient to evaluate the airway condition during tidal breathing.

Spirometry evaluates respiratory status during forced breathing, whereas IOS evaluates respiratory status during breathing at rest. In the patients with COPD and asthma, the increase or decrease of IOS and spirometric parameters were evaluated with respect to disease status. Our results showed that IOS and spirometry can evaluate the airway condition in patients with RP from different perspectives. Therefore, TrV could be evaluated from both perspectives.

This study has several limitations. RP is a rare disease and the number of patients with RP is small. Furthermore, we could not include approximately one-third of our patients with RP due to lack of data. We plan to start a prospective observational study for patients with RP. TrV was automatically measured using Ziostation2 software. Although the software was able to measure TrV during full inspiration, it could not accurately measure it during the expiratory phase. Therefore, improvements in the software are needed.

In conclusion, TrV and mtCSA were strongly correlated with spirometric measurements. However, respiratory resistances assessed by IOS were only correlated with TrV. TrV may be more appropriate than mtCSA to assess pulmonary function in patients with RP.

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Statement of Ethics

The Ethics Committee of St. Marianna University School of Medicine approved this retrospective study. The need for informed consent was waived.

Conflict of Interest Statement

Tsuneo Yamashiro received a research grant from Canon Medical Systems. The other authors do not have any conflicts of interest to disclose.

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The authors did not receive any funding.

Author Contributions

H.H. takes responsibility for the content of the manuscript, including the data and analysis. T.H. contributed substantially to the original concept, study design, data analysis and interpretation, and writing of the manuscript. Y.T. provided substantial contributions to interpretation of study data and critical review. H.H. and M.M. provided substantial oversight of the study design, data analysis, and provided critical revision of the manuscript. All authors reviewed and approved the final version of the manuscript.

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