

Chronic rhinosinusitis patients have decreased lung function

Shin Kariya, MD, PhD, Mitsuhiro Okano, MD, PhD, Takaya Higaki, MD, PhD, Yasuyuki Noyama, MD, Takenori Haruna, MD, Hisashi Ishihara, MD, Takuma Makino, MD, Tomoo Onoda, MD and Kazunori Nishizaki, MD, PhD

Background: The relationship between upper and lower airway diseases has been reported. However, the pulmonary function of patients with chronic rhinosinusitis (CRS) has not been fully examined.

Methods: Pulmonary function was measured in 273 patients with CRS and 100 age-matched normal control subjects. No patients with chronic obstructive pulmonary disease (COPD) were included in this study. The patients with CRS were divided into 8 subgroups based on the presence of asthma, sensitization to common inhaled antigens, and nasal polyposis. The relationships between pulmonary function and clinical parameters, including radiographic severity of CRS according to the Lund-Mackay computed tomography (CT) staging system, eosinophil count in the peripheral blood, and serum total immunoglobulin E (IgE) levels, were assessed.

Results: In pulmonary function testing, the CRS patients had affected pulmonary function. The CRS patients without asthma showed latent obstructive pulmonary function changes when compared to normal controls. No signifi-

cant correlations were observed between pulmonary function and any clinical parameters (Lund-Mackay CT staging score, eosinophil count in the peripheral blood, and serum total IgE levels).

Conclusion: CRS patients had significant obstructive lung function changes regardless of the presence of asthma. The patients with CRS who had not been clinically diagnosed as having lower respiratory tract diseases might have had sub-clinical lower airway diseases. Therefore, clinicians should be aware of pulmonary function and lower lung diseases in patients with CRS. © 2014 ARS-AAOA, LLC.

Key Words:

sinusitis; rhinitis; asthma; chronic obstructive pulmonary disease; pulmonary function

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A close link between upper and lower respiratory disease has been reported.¹ Chronic rhinosinusitis (CRS) and rhinitis are both common upper respiratory tract conditions among patients with asthma and chronic obstructive pulmonary disease (COPD).^{2,3} The impact of allergic rhinitis on asthma is well known; however, the effects of the affected paranasal sinus in lower airway disease manifes-

tations remains largely unclear.¹ Although numerous studies have reported a pathophysiologic link between allergic upper and lower airway disease, the relationship between nonallergic sinus disease and asthma or COPD has not yet been fully understood.⁴

Patients with asthma or COPD are known to have decreased pulmonary function; however, the pulmonary function of patients with upper respiratory tract disease has not been elucidated. Therefore, the present study aimed to characterize the pulmonary function of CRS patients, especially those without asthma, in comparison to healthy subjects.

Patients and methods

Subjects

A total of 273 patients with CRS who received endoscopic sinus surgery at Okayama University were recruited. The diagnosis of CRS was based on the definition in European Position Paper on Rhinosinusitis and Nasal Polyps 2012.⁵ Among these 273 patients with CRS, 70 patients had

Department of Otolaryngology-Head and Neck Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

Correspondence to: Shin Kariya, MD, PhD, Department of Otolaryngology-Head and Neck Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan; e-mail: skariya@cc.okayama-u.ac.jp

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asthma (57 patients with nasal polyposis; 13 patients without nasal polyposis) and 203 patients were subjects with no previous diagnosis of asthma (135 patients with nasal polyposis; 68 patients without nasal polyposis).

All CRS patients were resistant to medical treatment, including macrolide therapy.⁶ CRS patients with COPD were excluded from this study.

Age-matched normal control subjects ($n = 100$) without any chronic respiratory diseases were also recruited. Because cigarette smoking affects pulmonary function, smoking status and the Brinkman index (number of cigarettes per day $\times$ number of years of smoking) were examined. Informed consent was obtained from enrolled subjects. The protocol of this study was approved by the Institutional Review Board of Okayama University and all procedures were carried out in compliance with the Declaration of Helsinki of 1995 (as revised in 2008).

Pulmonary function testing

Before endoscopic sinus surgery, pulmonary function testing was performed with the CHESTAC-9800 (CHEST M.I., Inc., Tokyo, Japan) according to the standardization of pulmonary function tests of the American Thoracic Society and European Respiratory Society.⁷ The following parameters were measured or calculated: percent predicted vital capacity (%VC), forced expiratory volume in 1 second (FEV_{1.0}), percent predicted FEV_{1.0} (%FEV_{1.0}), FEV_{1.0}/forced vital capacity ratio (FEV_{1.0}/FVC ratio), mean forced expiratory flow between 25% and 75% of the forced vital capacity (FEF_{25%-75%}), peak expiratory flow (PEF), maximal expiratory flow rate at 50% of vital capacity (V₅₀), maximal expiratory flow rate at 25% of vital capacity (V₂₅), and the V₅₀/V₂₅ ratio.

CRS assessment by computed tomography staging

The radiographic severity of CRS was assessed according to the Lund-Mackay computed tomography (CT) staging system before endoscopic sinus surgery.⁸

Peripheral blood eosinophil count, total immunoglobulin E (IgE) level, and specific IgE level in serum samples

Blood samples were collected before endoscopic sinus surgery. The eosinophil count in the peripheral blood was determined. In serum samples, the total IgE and specific IgE to 13 allergens (*Dermatophagoides pteronyssinus*, *Felis domesticus*, *Canis familiaris*, *Dactylis glomerata*, *Aspergillus fumigatus*, *Candida albicans*, *Alternaria alternata*, *Trichophyton rubrum*, *Alnus incana*, *Cupressus japonica*, *Chamaecyparis obtusa*, *Ambrosia elatior*, and *Artemisia vulgaris*) were measured using the ImmunoCap 250 system (Phadia AB, Uppsala, Sweden) according to the manufacturer's protocols.

TABLE 1. Clinical parameters of pulmonary function in patients with chronic rhinosinusitis and normal control subjects

	Chronic rhinosinusitis with asthma	Chronic rhinosinusitis without asthma	Control
Subjects (n)	70	203	100
%VC	110.1 $\pm$ 16.5	112.6 $\pm$ 15.8	113.5 $\pm$ 11.7
FEV _{1.0}	2.4 $\pm$ 0.9*	3.3 $\pm$ 0.8	3.3 $\pm$ 0.7
%FEV _{1.0}	89.0 $\pm$ 19.2*	100.3 $\pm$ 15.5*	105.9 $\pm$ 10.5
FEV _{1.0} /FVC ratio	68.9 $\pm$ 10.9*	81.6 $\pm$ 8.3*	85.2 $\pm$ 6.3
FEF _{25%-75%}	1.57 $\pm$ 1.04*	3.06 $\pm$ 1.26*	3.70 $\pm$ 1.11
PEF	6.30 $\pm$ 2.08*	7.87 $\pm$ 1.88*	8.45 $\pm$ 2.27
V ₅₀	1.90 $\pm$ 1.18*	3.63 $\pm$ 1.32*	4.19 $\pm$ 1.14
V ₂₅	0.61 $\pm$ 0.47*	1.42 $\pm$ 0.80*	1.71 $\pm$ 0.84
V ₅₀ /V ₂₅ ratio	3.68 $\pm$ 1.79*	3.06 $\pm$ 1.64*	2.75 $\pm$ 0.86

Data represent means $\pm$ standard deviation.

* $p < 0.05$ as compared with normal control.

%FEV_{1.0} = percent predicted FEV_{1.0}; %VC = percent predicted vital capacity; FEF_{25%-75%} = mean forced expiratory flow between 25% and 75% of the forced vital capacity; FEV_{1.0} = forced expiratory volume in one second; FVC = forced vital capacity; PEF = peak expiratory flow; V₂₅ = maximal expiratory flow rate at 25% of vital capacity; V₅₀ = maximal expiratory flow rate at 50% of vital capacity.

Statistical analysis

All values are presented as means $\pm$ standard deviation. Differences in proportions were tested by the chi-square test. For comparisons between 3 or more groups, a 1-way analysis of variance (ANOVA) was performed to establish the significance of intergroup variability, and 2-tailed unpaired t tests were then used for between-group comparisons. Correlations were analyzed using Pearson's correlation coefficient. Values of $p < 0.05$ were considered statistically significant. All statistical analyses were performed using IBM SPSS statistical software (IBM, Armonk, NY).

Results

Pulmonary function in CRS patients with and without asthma

The pulmonary function of CRS patients with and without asthma and normal control subjects is shown in Table 1. No significant difference in %VC was observed between CRS patients and normal controls. In CRS patients with asthma, FEV_{1.0} was significantly smaller than in CRS patients without asthma and normal control subjects ($p < 0.05$). There were statistically significant differences in %FEV_{1.0}, FEV_{1.0}/FVC ratio, FEF_{25%-75%}, PEF, V₅₀, V₂₅, and V₅₀/V₂₅ ratio among all 3 groups ($p < 0.05$). Impaired pulmonary function was observed even in CRS patients without asthma or COPD.

TABLE 2. The characteristics of patients and normal controls

	Chronic rhinosinusitis with asthma				Chronic rhinosinusitis without asthma				Control	p
Sensitization to inhaled allergens	Positive		Negative		Positive		Negative			
Nasal polyposis	Present	Absent	Present	Absent	Present	Absent	Present	Absent		
Subjects (n)	48	8	9	5	98	55	37	13	100	
Gender (male/female) (n)	29/19	4/4	3/6	2/3	66/32	36/19	25/12	5/8	51/49	0.101*
Age (years)	44.0 ± 10.8	38.7 ± 10.2	47.4 ± 11.4	46.7 ± 6.4	36.9 ± 11.8	39.4 ± 11.8	38.8 ± 12.4	40.1 ± 10.0	38.7 ± 10.8	0.053**
Smoking status (n)										0.103*
Past smoker	17	2	2	2	19	9	7	3	25	
Current smoker	3	1	0	0	27	15	13	5	20	
Nonsmoker	28	5	7	3	52	31	17	5	55	
Brinkman index										
All smoker	540.5 ± 477.4	256.7 ± 127.4	105.0 ± 134.4	280.0 ± 56.6	349.2 ± 273.1	462.0 ± 317.0	462.7 ± 364.5	366.9 ± 292.8	313.2 ± 289.3	0.156**
Past smoker	568.8 ± 487.0	330.0 ± 14.1	105.0 ± 134.4	280.0 ± 56.6	333.2 ± 282.7	433.6 ± 352.7	432.9 ± 323.9	220.0 ± 163.7	307.0 ± 301.5	0.347**
Current smoker	379.7 ± 471.8	100	N/A	N/A	360.5 ± 271.0	479.0 ± 305.2	478.8 ± 396.4	455.0 ± 332.7	321.0 ± 280.9	0.600**

Data represent means ± standard deviation.

*Chi-square test.

**One-way analysis of variance

Brinkman index = number of cigarettes per day × number of years of smoking; N/A = not applicable.

Effect of sensitization to inhaled allergens and nasal polyposis on pulmonary function

As allergic status and nasal polyposis might have a critical effect on pulmonary function, we grouped the patients with CRS based on sensitization to common inhaled antigens and nasal polyposis. The patients were defined as sensitized if specific IgE levels were equal to or greater than 0.35 U_A/mL for at least 1 of the 13 inhaled antigens.

The clinical characteristics of the subjects are summarized in Table 2. There were no significant age differences among the groups. The current smoking rate in asthmatic CRS patients (sensitization positive, 7.1%, 4/56; sensitization negative, 0%, 0/14) was smaller than in nonasthmatic CRS patients and in normal control subjects. No statistically significant difference in smoking habits and the Brinkman index was observed between the groups.

The pulmonary function of each of the 9 groups is shown in Figure 1. No significant difference in %VC was observed between CRS patients and normal controls (Fig. 1A). When compared with normal controls, the asthmatic patients showed affected pulmonary function in FEV_{1.0}, %FEV_{1.0}, FEV_{1.0}/FVC ratio, FEF_{25%-75%}, PEF, V₅₀, V₂₅, and V₅₀/V₂₅ ratio, regardless of sensitization status (Fig. 1B-I). Significant differences in %FEV_{1.0}, FEV_{1.0}/FVC ratio, FEF_{25%-75%},

V₅₀, and V₂₅ were observed between the nonasthmatic CRS patients and normal controls (Figs. 1C-E, G, and H).

Serum total IgE levels

Serum total IgE levels of the subjects are summarized in Table 3. The CRS patients with sensitization had a significantly higher IgE level compared with the CRS patients without sensitization ($p < 0.05$). No statistically significant correlation was observed between serum total IgE levels and lung function.

Peripheral blood eosinophil count

Peripheral blood eosinophil counts of the subjects are summarized in Table 3. Nonasthmatic CRS patients with sensitization and nasal polyps and asthmatic patients had a significantly higher eosinophil count when compared with normal control subjects ($p < 0.05$). No statistically significant correlation was observed between peripheral blood eosinophil count and lung function.

The Lund-Mackay CT score

The Lund-Mackay CT scores of the subjects are summarized in Table 3. The CRS patients with nasal polyposis had significantly higher Lund-Mackay CT scores compared to

the CRS patients without nasal polyposis ($p < 0.05$). No statistically significant correlation was observed between Lund-Mackay CT score and lung function.

Discussion

CRS is characterized by inflammation of the nose and paranasal sinuses of unknown cause defined on the

basis of characteristic symptoms (2 or more of the following: nasal congestion, facial pain/pressure, anterior or posterior nasal drainage, and reduced or absent sense of smell), duration (more than 12 weeks), and objective evidence of sinus disease by means of direct visualization or imaging studies. CRS is a common disease, and affects 12.5% of the U.S. population or approximately 31 million patients each year.^{9,10}

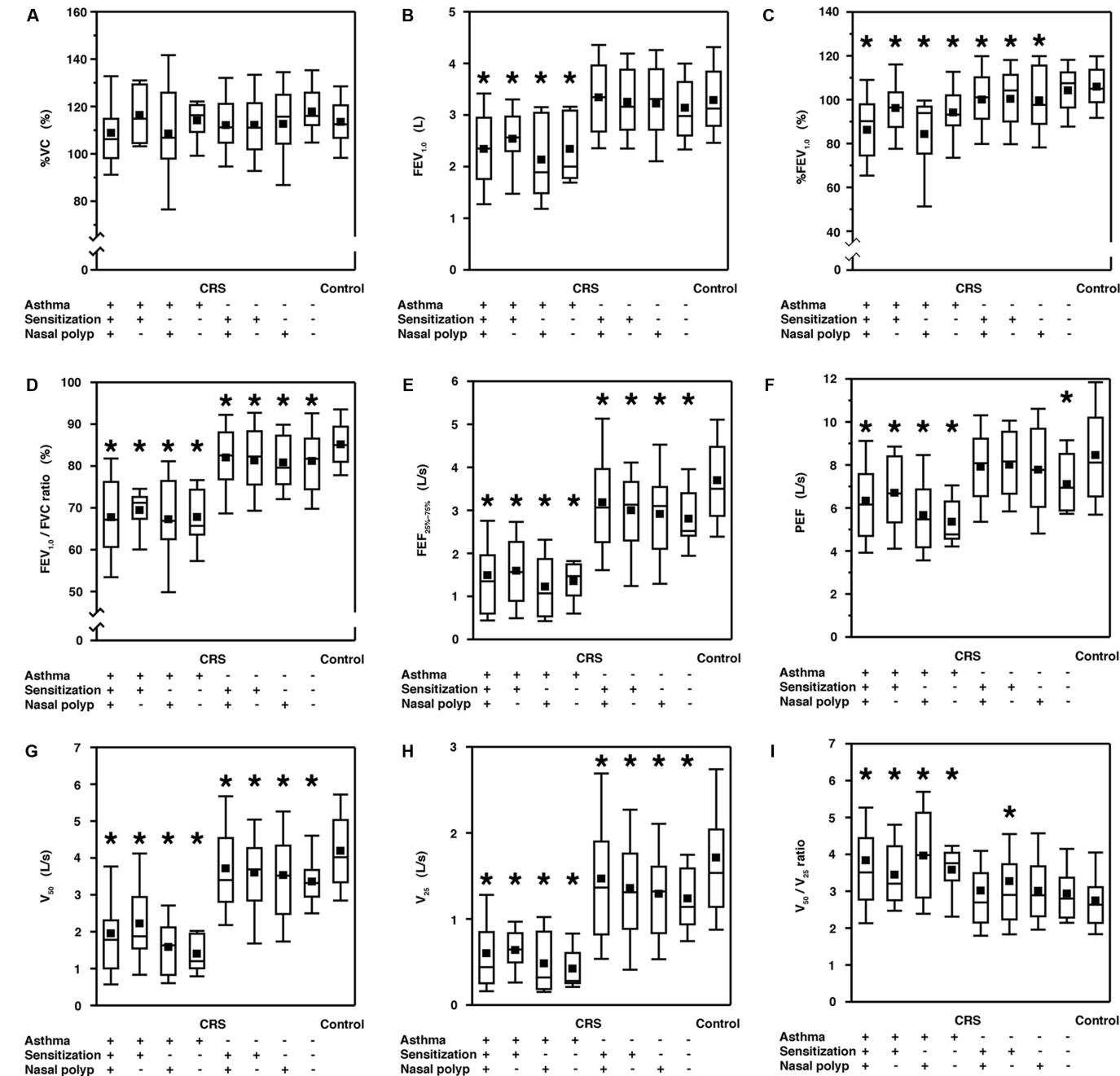


FIGURE 1. Pulmonary function in patients with chronic rhinosinusitis (CRS). (A) %VC. (B) FEV_{1.0}. (C) Percent predicted FEV_{1.0}. (D) FEV_{1.0}/FVC ratio. (E) FEF_{25%-75%}. (F) PEF. (G) V₅₀. (H) V₂₅. (I) V₅₀/V₂₅ ratio. The rectangle includes the range from the 25th to the 75th percentiles, the horizontal line indicates the median, and the vertical line indicates the range from the 10th to the 90th percentiles. The black square shows the mean value. *Indicates significant difference compared with normal controls. %VC = percent predicted vital capacity; FEF_{25%-75%} = mean forced expiratory flow between 25% and 75% of the forced vital capacity; FEV_{1.0} = forced expiratory volume in 1 second; FVC = forced vital capacity; PEF = peak expiratory flow; V₂₅ = maximal expiratory flow rate at 25% of vital capacity; V₅₀ = maximal expiratory flow rate at 50% of vital capacity.

TABLE 3. Clinical parameters of patients and normal controls

	Chronic rhinosinusitis with asthma				Chronic rhinosinusitis without asthma				Control	p
Sensitization to inhaled allergens	Positive		Negative		Positive		Negative			
Nasal polyposis	Present	Absent	Present	Absent	Present	Absent	Present	Absent		
Serum total IgE levels (IU/mL)	445.9 ± 498.8	352.0 ± 658.7	114.6 ± 93.3	242.0 ± 183.1	362.6 ± 521.7	462.0 ± 547.1	60.1 ± 62.3	62.7 ± 83.0	N/A	0.001*
Peripheral blood eosinophil count	749.1 ± 433.8	328.6 ± 175.3	585.2 ± 310.7	571.1 ± 473.7	391.1 ± 335.8	206.5 ± 168.2	214.6 ± 174.0	182.7 ± 146.9	165.4 ± 75.6	<0.001*
Lund-Mackay CT score	18.5 ± 4.8	6.0 ± 4.7	18.4 ± 5.1	13.6 ± 8.1	11.5 ± 5.5	6.8 ± 4.5	12.2 ± 6.5	6.4 ± 3.9	N/A	<0.001*

Data represent means ± standard deviation.

*One-way analysis of variance.

CT = computed tomography; IgE = immunoglobulin E; N/A = not applicable.

Epidemiological and pathophysiological connections between CRS and lower lung diseases have been suggested.^{11–14} Allergic rhinitis and its impact on asthma has been thoroughly studied; however, the relationship between nonallergic sinus disease and asthma is not yet fully understood.^{4,15} Some clinical studies have shown that the treatment of CRS, including medical or endoscopic sinus surgery, demonstrated a beneficial effect on the symptoms of concomitant asthma.^{16–19} This study revealed that CRS patients had affected lung function regardless of asthma. Although the subjects in this study were not clinically diagnosed as having COPD, CRS patients without asthma had latent obstructive lung function.

Total serum IgE levels and peripheral blood eosinophil counts are widely examined, and are remarkable biomarkers for evaluating patients with asthma.²⁰ This study showed that nonasthmatic CRS patients with sensitization and asthmatic patients had a statistically increased eosinophil count and high serum IgE level. These findings suggest that similar inflammatory processes are involved in both CRS with allergic sensitization and asthma. In addition, we also found that nonasthmatic CRS patients without sensitization did not show increased total serum IgE levels and peripheral blood eosinophil counts, but had latent obstructive lung function. These findings suggest that nonallergic sinus disease might be related to obstructive lower respiratory disease.

The Lund-Mackay CT score is widely used for assessing the disease severity of CRS.⁸ Mehta et al.²¹ reported that blood and sputum eosinophil levels in patients with asthma are directly correlated with sinus mucosal thickening assessed by Lund-Mackay CT score. In the present study, we observed that CRS patients with nasal polyposis had a higher Lund-Mackay CT score than CRS patients without nasal polyposis.

Various explanations for the upper and lower airway association in the pathogenesis of united airway diseases have been presented. These hypotheses include the systemic reactions, nasobronchial reflex, pharyngobronchial reflex, postnasal drainage of inflammatory mediators from the upper to lower airways, and inhalation of dry, cold air and environmental pollutants.^{4,15,22,23} Clinical parameters in this study (IgE levels, peripheral blood eosinophil counts, and CT score) did not significantly correlate with the spirometric parameters. A recent study showed that inflammatory cytokines in nasal secretion might be associated with decreased lung function.²⁴

The extent of the impact of upper respiratory disease on lower respiratory function is currently under debate. Dixon et al.²⁵ reported that asthmatics without rhinitis tend to have lower lung function than asthmatics with rhinitis. In contrast, another report showed that allergic rhinitis and sinusitis were associated with more severe asthmatic symptoms.²⁶ The present findings clearly show that CRS patients had affected lung function, even in patients who were not clinically diagnosed as having lower lung disease. Although the strong relationship between allergic rhinitis and asthma is well established, the effect of CRS on the pathogenesis of lower lung diseases remains controversial. Further investigation into the causes of loss of lung function in patients with CRS is required to clarify the relationship between upper and lower respiratory tract disorders.

Conclusion

This study showed that pulmonary function was affected in patients with CRS, regardless of sensitization status. The CRS patients without asthma or COPD had latent obstructive lung function changes. Clinicians should be aware of the condition of the lower respiratory tract in patients with CRS. 

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