



Contents lists available at ScienceDirect



Evaluation of airway hyperresponsiveness in chronic rhinosinusitis: values of sinus computed tomography

Fenghong Chen, MD^{*}; Xiangqian Luo, MD^{*}; Rui Xu, MD, PhD^{*}; Jie Deng, MD^{*}; Kejun Zuo, MD^{*}; Huabin Li, MD, PhD[†]; and Jianbo Shi, MD, PhD^{*}

^{*} Allergy and Cancer Center, Otorhinolaryngology Hospital, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China

[†] Department of Otolaryngology, Head and Neck Surgery, Xinhua Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China

ARTICLE INFO

Article history:

Received for publication June 20, 2014.

Received in revised form September 9, 2014.

Accepted for publication September 10, 2014.

ABSTRACT

Background: Chronic rhinosinusitis (CRS) is tightly linked to airway hyperresponsiveness (AHR) and asthma. However, the practical surrogate parameters for evaluating AHR in patients with CRS remain unclear.

Objectives: To evaluate the diagnostic values of sinus computed tomography for AHR in patients with CRS. **Methods:** We performed a prospective, single-blinded study of 125 consecutive patients with CRS. These patients were subdivided into AHR and non-AHR (NAHR) groups based on histamine provocation test results. The following parameters were compared between 2 groups of CRS patients: Lund-Mackay scores, olfactory cleft (OC) scores, and serum eosinophil counts.

Results: Fifty-seven patients (45.4%) presented with AHR. The OC scores, the ratio of OC scores to total scores, and the eosinophil counts in the AHR group were significantly higher than those in the NAHR group ($P < .001$). Multivariate logistic regression revealed that OC scores and eosinophil counts were independent risk factors for asymptomatic AHR (OC scores $P < .001$ and eosinophil counts $P = .010$). The OC score had a higher predictive value for AHR (area under curve, 0.800) than eosinophil counts (area under the curve, 0.637). When the OC score was 3 or higher, the sensitivity was 75.0%, specificity was 77.9%, and positive predictive value was 68.8%.

Conclusion: The findings validate a prospective assessment of sinus computed tomography as a screening tool for AHR in patients with CRS.

© 2014 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Introduction

Chronic rhinosinusitis (CRS) is a chronic inflammatory disease of the upper airway that is tightly linked to lower respiratory tract disorders, such as asthma. Airway hyperresponsiveness (AHR), the main feature of asthma, stems from an ongoing inflammatory and remodeling process of an undetermined origin. Epidemiologic data indicate that patients with asymptomatic AHR (AAHR) are at a high risk of developing asthma.^{1,2} The proportion of asthma and AAHR increases in patients with CRS when compared with a general Western population.^{3,4} However, data on the proportion of AAHR in Asian patients with CRS are limited.

Reprints: Jian-Bo Shi, MD, PhD, Otorhinolaryngology Hospital, the First Affiliated Hospital, Sun Yat-Sen University, 58 Zhongshan Road II, Guangzhou, Guangdong, People's Republic of China 510080; E-mail: shijb@mail.sysu.edu.cn or Huabin Li, MD, PhD, Department of Otolaryngology, Head and Neck Surgery, Xinhua Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China; E-mail: allergyli@163.com.

Disclosures: Authors have nothing to disclose.

Funding: This study was supported by grant 201202005 from the Industry Foundation of the Ministry of Health in China.

<http://dx.doi.org/10.1016/j.anai.2014.09.006>

1081-1206/© 2014 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Studies focusing on how to detect AHR in patients with CRS are limited. Only blood eosinophil counts and nasal symptoms have been used to predict AHR in patients with nasal polyps (NPs) with moderate sensitivity and specificity.⁵ Although the use of sinus computed tomography (CT) in patients with CRS and coexisting asthma has been well described in the literature,^{6–8} the sinus CT findings in AAHR patients have not been delineated yet. On the other hand, the olfactory cleft (OC) score is a predictor of eosinophil CRS (ECRS), and asthma comorbidity is a risk factor for ECRS.⁹ However, it is unclear whether sinus CT score and OC scores can predict AHR in CRS. The aims of this study were to evaluate the sinus CT features of patients with CRS and AHR and the diagnostic values of sinus CT scores for predicting AHR in patients with CRS. We theorized that patients with CRS and AHR had specific sinus CT features that could identify their AHR.

Methods

Study Participants

This study enrolled 125 consecutive CRS patients (≥ 18 years old) undergoing functional endoscopic sinus surgery in Otorhinolaryngology

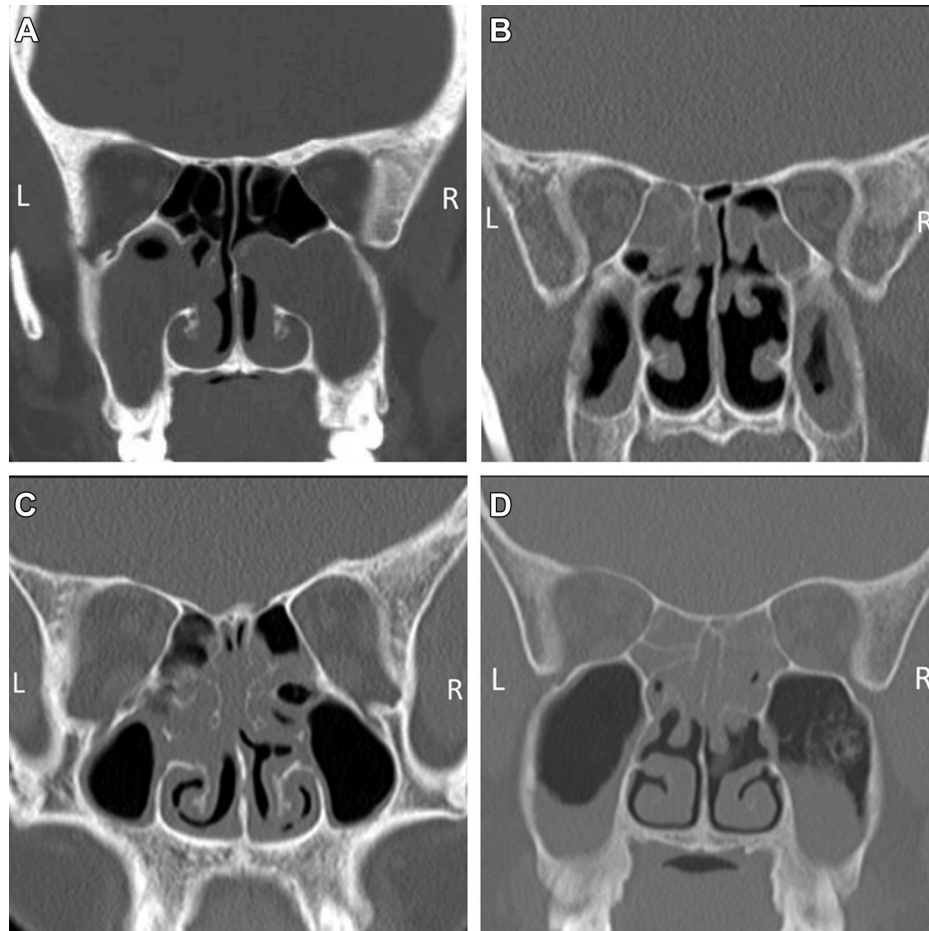


Figure 1. Olfactory cleft (OC) score was observed on the posterior ethmoid sinus and superior turbinate level. A, Each OC score was 0. B, Left OC score was 0, right OC score was 2, and total OC score was 2. C, Each OC score was 1, and total OC score was 2. D, Each OC score was 2, and total OC score was 4.

Hospital, First Affiliated Hospital of Sun Yat-sen University, between September 2012 and August 2013. The diagnosis of CRS was based on a European position paper on rhinosinusitis and NPs.¹⁰ Patients were excluded if they had any respiratory disease except asthma (eg, chronic obstructive pulmonary disease); had acute respiratory infection in 4 weeks; or had taken any corticosteroids (systemic and local), antihistamines (systemic and local), leukotriene receptor antagonists, β_2 -receptor agonists, or anticholinergic agents within the 2 weeks before the bronchial provocation test. Patients avoided smoking, cold air, and strenuous exercise. The study had ethical approval from the institutional review board of the First Affiliated Hospital of Sun Yat-sen University. All participants provided written informed consent to participate in this study.

Study Design

This prospective, single-blinded study collected information on asthma history. All patients except those diagnosed as having asthma were subjected to lung expiratory volume tests and bronchial provocation and dilation tests and then divided into AHR and non-AHR (NAHR) groups according to the test results. AHR were defined as a 20% or greater reduction in the forced expiratory volume in 1 second after serial administration of histamine up to a concentration of 8 mg/mL or less. The patients with diagnosed asthma were enrolled in the AHR group. The patients without diagnosed asthma were carefully questioned about the presence of recurrent symptoms of asthma, including wheezing, coughing, chest tightness, and shortness of breath. The patients without these symptoms but with positive provocation test results were enrolled

in the AAHR. The following parameters between groups were compared: sinus CT, blood eosinophil number and ratio, and concurrent allergic rhinitis and NPs.

CT and Sinus Score

Study participants underwent sinus CT examination in a supine position. The CT examination collected 1-mm axial images, which were reconstructed offline and reformatted to 3-mm coronal images for analysis (Toshiba Aquilion, Tokyo, Japan). Sinus CTs were reviewed by an investigator masked to the patients' clinical condition. CT scoring was based on the Lund-Mackay scoring system,¹¹ supplemented with the OC score. In the Lund-Mackay staging system, which is based on a simple numeric score derived from the CT, each sinus group is assigned a numeric grade: 0, no abnormality; 1, partial opacification; and 2, total opacification. The sinus groups include the maxillary sinus, frontal sinus, sphenoid sinus, anterior ethmoid sinus, and posterior ethmoid sinuses. The ostiomeatal complex is scored as 0 (not obstructed) or 2 (obstructed). The OC score was observed on the posterior ethmoid sinus and superior turbinate level. Each OC was awarded 0 to 2 points: 0, no abnormality; 1, partial opacification; and 2, total opacification (Fig 1).⁹ The total score was the Lund-Mackay total scores supplemented with the OC scores, producing a maximum of 28 points.

Statistical Analysis

SPSS statistical software, version 16.0 (SPSS Inc, Chicago, Illinois), was used for statistical analyses. Continuous variables are

Table 1
Demographic data and serum eosinophil counts of patients with AHR and NAHR

Variable	AHR (n = 57)	NAHR (n = 68)	P value ^a
Female, No. (%)	22 (38.6)	15 (22.1)	.04
Age, mean (SD), y	44.61 (12.92)	40.75 (12.68)	.10
Nasal polyps, No. (%)	50 (87.7)	53 (77.9)	.15
AR, No. (%)	27 (47.4)	21 (30.9)	.06
Eosinophil count, mean (SD), cells/ μ L	351.40 (205.75)	194.61 (154.81)	<.001
Eosinophil ratio, mean (SD)	2.03 (2.82)	1.65 (2.35)	.48
ASA sensitivity, No. (%)	3 (5.26)	1 (1.47)	.22

Abbreviations: AHR, airway hyperresponsiveness; AR, allergy rhinitis; ASA, acetylsalicylic acid; NAHR, non-airway hyperresponsiveness.

^aP value by the unpaired *t* test for continuous variables and χ^2 test by categorical variables.

given as mean $\pm$ SD, and categorical variables are given as number (percentage) of the total population. The unpaired *t* test was used to compare mean values of the items with standard normal distributions between the AHR and NAHR groups. Categorical variables were analyzed with the χ^2 test. Because values of items were not normally distributed, the Mann-Whitney test for unpaired comparisons was used. Binary logistic regression analysis was performed for multivariate analysis of predictive factors of AAHR and odds ratio calculation, and asthma was excluded. The receiver operating characteristic curve analyzed the predict ability of OC scores and eosinophil counts. $P < .05$ was considered statistically significant.

Sample Size Calculation

The OC score and serum eosinophil count were major indexes in this study. Sample size estimation was based on these 2 indexes in the AHR and NAHR group. With $\alpha = .05$ and power = .80, the sample size of each group was calculated by the following formula: $n = [(Z_{\alpha/2} + Z_{\beta})^2 \times \{2(\hat{\sigma}^2)\}]/(\mu_1 - \mu_2)^2$, with *n* indicating the sample size required in each group; μ , mean; and $\hat{\sigma}$, SD.¹² In the results of a preliminary study, we found a mean (SD) OC score of 3.02 (1.47) in the AHR group and 1.14 (0.98) in the NAHR group; the sample size of each group must be at least 17 as calculated. The mean (SD) eosinophil count was 324.31 (222.10) in the AHR group and 203.58 (174.66) in the NAHR group; the sample size of each group must at least be 42 as calculated. We finally enrolled 57 patients in the AHR group and 68 patients in the NAHR group in the same period.

Results

There were 57 patients (45.4%) in the AHR group and 68 patients (54.4%) in the NAHR group. In the AHR group, 13 of the 57 patients (22.8%) had asthma, 2 of whom had been newly diagnosed as having asthma; 44 of 57 patients (77.2%) had AAHR. The proportion of female patients was higher in the AHR group than in the NAHR group (38.6% vs 22.1%, $P = .04$). Meanwhile, no significant difference was found between the 2 groups or age, concurrency of NPs, allergic rhinitis, and acetylsalicylic acid sensitivity. The mean value of the blood eosinophil counts was significantly higher in the AHR group than that in the NAHR group ($P < .001$) (Table 1).

For sinus Lund-Mackay scoring, the total score, OC score, posterior ethmoid sinuses score, anterior ethmoid sinuses scores, sphenoid sinus score, and osteomeatal complex score in the AHR group were significantly higher than in the NAHR group (total score and OC score: $P < .001$; posterior ethmoid sinuses score: $P = .003$; anterior ethmoid sinuses score: $P = .01$; sphenoid sinus score: $P = .01$; osteomeatal complex score: $P = .005$) (Table 2). The ratio of OC score was higher in the AHR group than in the NAHR group ($P < .001$). Conversely, the ratio of maxillary sinus scores to osteomeatal complex scores was higher in the NAHR group (maxillary sinus scores: $P = .003$; osteomeatal complex scores: $P = .01$). (Table 3).

Table 2
Mean (SD) sinus computed tomography scores for the AHR and NAHR groups

Variable	AHR	NAHR	P value ^a
Total score	19.84 (5.01)	15.08 (5.45)	<.001 ^b
Individual region			
Olfactory cleft	3.25 (1.32)	0.76 (1.47)	<.001
Ostiomeatal complex	3.73 (0.77)	3.36 (0.74)	.005
Maxillary sinuses	2.49 (0.69)	2.36 (0.89)	.84
Anterior ethmoid sinus	2.98 (0.89)	2.53 (0.93)	.01
Posterior ethmoid sinus	2.70 (0.88)	2.14 (1.04)	.003
Sphenoid sinuses	2.01 (1.44)	1.39 (1.23)	.01 ^b
Frontal sinuses.	2.66 (1.45)	2.50 (1.45)	.53
Ratio of region to total score			
Olfactory cleft	0.16 (0.07)	0.04 (0.08)	<.001
Ostiomeatal complex	0.20 (0.06)	0.23 (0.08)	.01 ^b
Maxillary sinuses	0.12 (0.03)	0.16 (0.07)	.003 ^b
Anterior ethmoid sinus	0.15 (0.04)	0.16 (0.06)	.11
Posterior ethmoid sinus	0.13 (0.03)	0.13 (0.05)	.52 ^b
Sphenoid sinuses	0.09 (0.06)	0.07 (0.06)	.19 ^b
Frontal sinuses.	0.13 (0.07)	0.14 (0.07)	.16

Abbreviations: AHR, airway hyperresponsiveness; NAHR, non-airway hyperresponsiveness.

^aP value of Mann-Whitney test except where indicated otherwise.

^bP value of the unpaired *t* test.

Multivariate logistic regression revealed that OC score and female sex were risk factors for AAHR (Table 3). Figure 2 displays the receiver operating characteristic curves for the OC scores and eosinophil counts. The OC score had a higher predictive value for AHR (area under the curve, 0.80) than the eosinophil counts (area under the curve, 0.637). Several cutoff points for these 2 predictors were selected. When the OC score was 3 or higher, the sensitivity was 75.0%, specificity was 77.9%, and positive predictive value was 68.8%. At the cutoff level of 255 cells/ μ L, the sensitivity and specificity of the eosinophil count were 63.6% and 67.6%, respectively, and positive predictive value was 56.0%.

Discussion

In the present work, as expected, we found that the OC score could be a predictor of AAHR in CRS patients. At an OC score of 3 or higher, the specificity reached 75.0% and the sensitivity was 77.9%. The sensitivity and specificity of the eosinophil count were 63.6% and 67.6%, respectively, at the cutoff level of 255 cells/ μ L. Han et al⁵ used an eosinophil count of 300 cells/ μ L as a cutoff value in patient with NPs to predict the AAHR; the sensitivity and specificity were both 70%. Although eosinophil counts had a moderate predictive value, the OC score was superior to the eosinophil count in the present study. In fact, this is the first study, to our knowledge, to reveal OC area opacification as a main feature of CRS with AHR and AAHR using sinus CT to detect AAHR.

Table 3
Multivariate logistic regression analysis of the predictive factors for AAHR

Predicting factor	OR (95% CI)	P value
Sex (female)	3.690 (1.231–11.055)	.02
Allergy rhinitis	0.899 (0.330–2.451)	.83
Nasal polyps	1.582 (0.410–6.112)	.51
Eosinophil count	14.575 (0.811–261.778)	.07
Total score	0.818 (0.813–1.177)	.98
Olfactory cleft	2.055 (1.541–2.740)	<.001
Anterior ethmoid sinus	1.002 (0.479–2.097)	>.99
Posterior ethmoid sinus	1.148 (0.474–2.782)	.76
Ostiomeatal complex	1.381 (0.733–2.604)	.32

Abbreviations: AAHR, asymptomatic airway hyperresponsiveness; CI, confidence interval; OR, odds ratio.

Binary logistic regression analysis was used for statistical analysis.

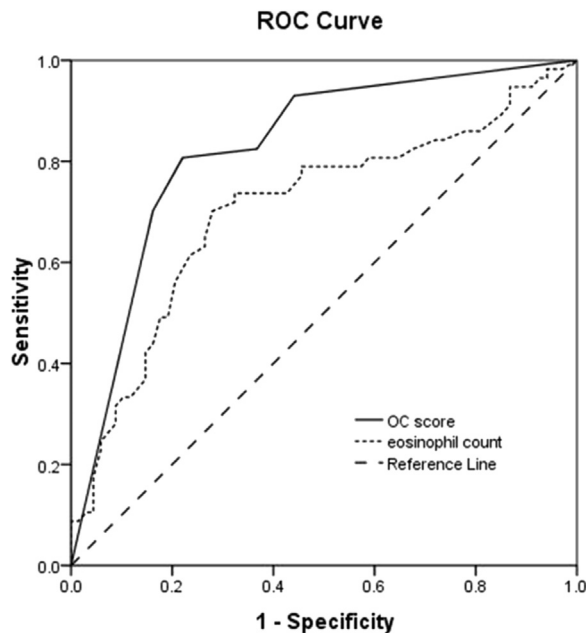


Figure 2. The receiver operating characteristic (ROC) curve for olfactory cleft (OC) score and eosinophil counts. Area under the ROC curve (AUC) of OC score was 0.80 (95% confidence interval, 0.718–0.886), and AUC of eosinophils counts was 0.637 (95% confidence interval, 0.527–0.746).

Our findings suggest that otolaryngologists should carefully ask about the presence of asthma symptoms in patients with increasing OC scores and serum eosinophil counts, especially in female patients, because some asthma symptoms are not usual (eg, only cough or chest tightness) and therefore may be ignored by patients. Asthma is underdiagnosed in CRS patients who undergo functional endoscopic sinus surgery, especially elderly patients.¹³ This method could help otolaryngologists screen for asthma in CRS patients. Moreover, AHR is a risk factor for corticosteroid insensitivity in patients with NPs.¹⁴ Evaluation AHR helps practitioners decide therapeutic schedules for CRS patients. Furthermore, because patients with uncontrolled asthma have a high risk of intraoperation bronchospasm,^{15,16} identifying asthma before surgery and intervention can increase the safety of the surgery. Last, one of the proposed mechanisms connecting asthma and CRS is that persistent upper airway inflammation releases proinflammatory mediators, which could stimulate bronchus and initiate AHR via nasobronchial reflex of direct aspiration pathways.^{17,18} Elucidating or alleviating this stimulation from upper airway possibly reverses this process.

This study includes a combination of CRS with NPs ($n = 106$ [84.8%]) or without NPs ($n = 19$ [15.2%]). Indeed, many previous studies suggest that CRS with NPs and CRS without NPs are separate diseases with separate pathophysiologic features and responses to therapy.¹⁹ This conclusion was driven in large part by research into these 2 subtypes that indicated a significant association between nasal polyposis and the presence of tissue eosinophilia. However, recent studies report that CRS is actually a heterogeneous disease entity composed of a spectrum of disorders.²⁰ Many experts claimed that although certain forms of CRS might be more likely to produce NPs, polyposis can develop as a complication of any form of CRS and should not be used as the exclusive basis for diagnosis or treatment recommendations for CRS.

Most studies found asthmatic patients with severe disease according to sinus CT. However, the involvement tendency of sinuses was conflicting.^{6–8} Dhong et al⁶ reported that the ratios of ethmoid sinus score to total score were higher in asthmatic patients than in

nonasthmatic patients, and the ratios of the score of maxillary sinus to total score were lower in asthmatic patients than in nonasthmatic patients. Conversely, Adapinar et al⁷ found that all individual scores of sinuses were significantly higher in asthmatic patients, except for the frontal sinus. These inconsistent results were possibly related to the small sample size of each study and the different evaluation methods.

The OC score was firstly described by Sakuma et al⁹. They used the OC score to detect ECRS in patients with NPs. (28.2% of whom also had asthma). However, they did not evaluate the airway responsiveness state. Although the Lund-Mackay scoring system is widely applied in evaluation of disease extent and severity of CRS, considering the role of the OC score in detecting AHR and ECRS, we recommend the modified Lund-Mackay scoring system with an added OC score. The mechanism of OC opacification in sinus CT is unclear. We suppose it is related to eosinophil inflammation. However, the details need to be further studied.

In addition, we found that the AHR increased to 45.4% in CRS patients in southern China (36.8% were asymptomatic and 10.4% had asthma). The incidence of asthma was only 3% in our previous study performed in 2010.²¹ AHR is increasing in southern China, and our data are consistent with data from South Korea. Han et al⁵ reported that 35% of NP patients had comorbid AAHR. The proportion of AHR in southern China is lower than in Western countries; however, the prevalence of AAHR was up to 50% in patients with NPs.^{4,14}

Despite some uncontrolled variables, such as the types of allergens and inflammation patterns, other unknown variables may have contributed to this study. In addition, pathologic evaluation of OC is needed to confirm the change in OC. Despite these limitations, this study may provide worthwhile information because statistical analysis evidenced striking differences of OC scores between AHR and NAHR patients. In conclusion, CRS with concomitant AHR has specific features on CT. Bilateral OC opacification is the most distinctive characteristic. OC score is a powerful tool to screen for AHR in CRS patients.

Acknowledgment

We thank Professor Chunquan Ou and Professor Xiaobo Guo for their advice in statistical analysis of this research.

References

- [1] Pattemore PK, Asher MI, Harrison AC, Mitchell EA, Rea HH, Stewart AW. The interrelationship among bronchial hyperresponsiveness, the diagnosis of asthma, and asthma symptoms. *Am Rev Respir Dis.* 1990;142:549–554.
- [2] Laprise C, Boulet LP. Asymptomatic airway hyperresponsiveness: a three-year follow-up. *Am J Respir Crit Care Med.* 1997;156:403–409.
- [3] Peat JK, Salome CM, Woolcock AJ. Factors associated with bronchial hyperresponsiveness in Australian adults and children. *Eur Respir J.* 1992;5: 921–929.
- [4] Mahut B, Plantier L, Malinvaud D, Chevalier-Bidaud B, Bonfils P, Delclaux C. Pathophysiology of airway hyperresponsiveness in patients with nasal polyposis. *Respir Med.* 2012;106:68–74.
- [5] Han DH, Kim SW, Cho SH, et al. Predictors of bronchial hyperresponsiveness in chronic rhinosinusitis with nasal polyp. *Allergy.* 2009;64:118–122.
- [6] Dhong HJ, Kim HY, Chung YJ, et al. Computed tomographic assessment of chronic rhinosinusitis with asthma. *Am J Rhinol.* 2006;20:450–452.
- [7] Adapinar B, Kurt E, Kebapci M, Erginel MS. Computed tomography evaluation of paranasal sinuses in asthma: is there a tendency of particular site involvement? *Allergy Asthma Proc.* 2006;27:504–509.
- [8] Kountakis SE, Bradley DT. Effect of asthma on sinus computed tomography grade and symptom scores in patients undergoing revision functional endoscopic sinus surgery. *Am J Rhinol.* 2003;17:215–219.
- [9] Sakuma Y, Ishitoya J, Komatsu M, et al. New clinical diagnostic criteria for eosinophilic chronic rhinosinusitis. *Auris Nasus Larynx.* 2011;38:583–588.
- [10] Fokkens WJ, Lund VJ, Mullol J, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012: a summary for otorhinolaryngologists. *Rhinology.* 2012;50:1–12.
- [11] Lund VJ, Kennedy DW. Staging for rhinosinusitis. *Otolaryngol Head Neck Surg.* 1997;117:S35–X40.

- [12] Sakpal TV. Sample size estimation in clinical trial. *Perspect Clin Res*. 2010;1: 67–69.
- [13] Tanaka S, Hirota T, Kamijo A, et al. Lung functions of Japanese patients with chronic rhinosinusitis who underwent endoscopic sinus surgery. *Allergol Int*. 2014;63:27–35.
- [14] Bonfils P, Avan P. Non-specific bronchial hyperresponsiveness is a risk factor for steroid insensitivity in nasal polyposis. *Acta Otolaryngol*. 2004;124:290–296.
- [15] Smetana GW, Conde MV. Preoperative pulmonary update. *Clin Geriatr Med*. 2008;24:607–624.
- [16] Asaka D, Nakayama T, Hama T, et al. Risk factors for complications of endoscopic sinus surgery for chronic rhinosinusitis. *Am J Rhinol Allergy*. 2012;26: 61–64.
- [17] Corren J. Allergic rhinitis and asthma: how important is the link? *J Allergy Clin Immunol*. 1997;99:S781–S786.
- [18] McFadden EJ. Nasal-sinus-pulmonary reflexes and bronchial asthma. *J Allergy Clin Immunol*. 1986;78:1–3.
- [19] Payne SC, Borish L, Steinke JW. Genetics and phenotyping in chronic sinusitis. *J Allergy Clin Immunol*. 2011;128:710–722.
- [20] Meltzer EO, Hamilos DL. Rhinosinusitis diagnosis and management for the clinician: a synopsis of recent consensus guidelines. *Mayo Clin Proc*. 2011;86: 427–443.
- [21] Fan Y, Chen S, Qu X, et al. A lower prevalence of asthma among patients with chronic rhinosinusitis in southern China. *J Allergy Clin Immunol*. 2011;127: 520–522.