

Patients with chronic rhinosinusitis and simultaneous bronchial asthma suffer from significant extraesophageal reflux

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Background: The aim of this study was to determine the severity of extraesophageal reflux (EER) in patients with various degrees of chronic rhinosinusitis (CRS), and particularly in patients with simultaneous bronchial asthma.

Methods: Patients with different severity of CRS were invited to participate in the study. Group I consisted of patients with CRS without nasal polyps or bronchial asthma; group II consisted of patients with CRS with nasal polyps but without bronchial asthma; group III consisted of patients with CRS with nasal polyps and bronchial asthma. The age, gender, Reflux Symptom Index, severity of EER evaluated using the Restech system, and number of previous functional endoscopic sinus surgeries (FESSs) were compared between groups.

Results: A total of 90 patients (30 in each group) were recruited for the study. Pathological EER was significantly often present in group III when compared with group I and group II in all parameters analyzed (RYAN score, number

of EER episodes, total percentage of time below pH 5.5). Furthermore, patients from group III had undergone more surgeries in the past.

Conclusion: Patients with CRS with nasal polyps and simultaneous bronchial asthma suffer from significant EER. Antireflux therapy can be recommended for these patients. However, the effect has to be confirmed in further studies.
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Key Words:

chronic rhinosinusitis; extraesophageal reflux; oropharyngeal pH monitoring; bronchial asthma; antireflux therapy

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Chronic rhinosinusitis (CRS) is 1 of the most common chronic diseases affecting adults in the United States.^{1,2} Despite intensive conservative as well as surgical treatment, some patients do not respond to standardized protocols appropriately, and suffer from so called refractory CRS.^{3,4} Many factors have been cited as possible rea-

sons for this; eg, immunodeficiency, fungal sinusitis, bacterial biofilms, vasculitis, structural abnormalities, cystic fibrosis, sarcoidosis, and others.^{4–6}

During the last decade, extraesophageal reflux (EER) has been hypothesized to be 1 of the possible factors contributing to the worsening of CRS.⁷ To date, only a few studies have tried to elucidate the relationship between CRS and reflux.^{8–18} In most of them, history and/or esophageal pH monitoring has been used to determine the presence and severity of gastroesophageal and extraesophageal reflux. The results of these studies suggest that patients with refractory CRS and CRS which persists after functional endoscopic sinus surgery (FESS) have more hypopharyngeal or nasopharyngeal reflux episodes when compared with patients who have no recurrence after FESS.^{8–13} Moreover, treatment of reflux led to improvement of refractory CRS in some studies.^{16–18} Despite these promising results, the relationship between EER and CRS remains indeterminate due to its complexity; it is not clear whether antireflux treatment is indicated for those patients and who would benefit from it. According to the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS), evidence of a relationship

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between CRS and EER is at level III, and further study of the relationship is recommended.¹⁹

An analogous medical dilemma involves the relationship between bronchial asthma and EER. Many patients with bronchial asthma suffer from reflux (30–90%), but questions remain about their treatment with proton pump inhibitors (PPIs). It is still not clear how to select asthmatic patients with EER who would best respond to antireflux therapy.^{20–23} Therefore, identifying the characteristics of a reflux-related asthma phenotype is very important, and more research is needed in this area.²¹

The aim of the present study was to determine the severity of EER in patients with various degrees of CRS, and particularly in patients with simultaneous bronchial asthma. Such a study has not been performed to date. We assumed that patients with simultaneous CRS and bronchial asthma would suffer from the most severe reflux and would therefore be good candidates for antireflux therapy.

Patients and methods

This prospective case-series study was approved by the Ethics Committee of the University Hospital Ostrava and was performed in accordance with the Declaration of Helsinki, good clinical practice, and applicable regulatory requirements. The study was registered on ClinicalTrials.gov under the identifier NCT01819454. Written informed consent was obtained from all subjects before initiating any procedure.

Study design

Patients with different degrees of severity of CRS were invited to participate in the study. Participants were divided into 3 groups. Group I consisted of patients with CRS without nasal polyps or bronchial asthma; group II consisted of patients with CRS with nasal polyps but without bronchial asthma; group III consisted of patients with CRS with nasal polyps and bronchial asthma. We decided to include 30 patients in each group to have homogeneous groups for further statistical analysis.

Inclusion criteria

Patients 18 to 64 years old who were followed at the Ear/Nose/Throat (ENT) clinic of a tertiary hospital, who had been diagnosed with CRS with/without nasal polyps (according to the EPOS definition),¹⁹ and had been scheduled for FESS for persistent symptoms of CRS were invited to participate in the study. Only patients who had been treated with nasal topical corticosteroids for at least the 2 years prior to the study and who had been put on systemic steroids (20 mg of prednisolone daily for 10 days) at least twice during the second of the 2 years were invited to participate. Only nonsmokers were asked to participate in the study. Patients with simultaneous bronchial asthma were enrolled in group III. Only patients with a diagnosis of bronchial asthma made by a respiratory physician

and who had been treated with inhaled corticosteroids for at least the 2 years prior to the study were included. If patients had undergone FESS in the past, only those who were operated on in our department were enrolled in the study. All patients underwent preoperative computed tomography (CT) scan, which showed polypoid thickening of the sinus mucosa, and the diagnosis of CRS was confirmed during consecutive FESS.

Exclusion criteria

Patients with prediagnosed cystic fibrosis based on a positive sweat test or DNA alleles, immunodeficiency (congenital or acquired), congenital mucociliary problems (eg, primary ciliary dyskinesia), noninvasive fungal balls and invasive fungal disease, systemic vasculitis and granulomatous diseases, and neoplasia of the nose or sinuses were excluded from the study.

Demographic data and history

The age, gender, history of nasal and systemic corticosteroid therapy, history of bronchial asthma and its treatment with inhaled corticosteroids, and number of FESSs (no surgery, 1 to 2 surgeries, 3 or more surgeries) within the previous 5 years was ascertained. In addition, patients were asked to complete the Reflux Symptom Index (RSI) questionnaire introduced by Belafsky et al.²⁴ The RSI questionnaire is standardized and widely used in the assessment of EER symptoms.

Twenty-four-hour monitoring of oropharyngeal pH

Twenty-four-hour monitoring of oropharyngeal pH was carried out 24 to 36 hours prior to the FESS using the Restech® system (Respiratory Technology Corporation, San Diego, CA). The Restech pH catheter was calibrated in solutions of pH 7 and pH 4 prior to use. The sensor was inserted through the nasal cavity until the flashing light-emitting diode (LED) was seen in the back of the subject's throat and then positioned so that the flashing light was 5 to 10 mm below the uvula. The catheter was secured to the patient's face and then passed over the ear and secured to the neck. The transmitter at the end of the catheter was either taped to the skin or attached to the subject's clothing using a clip-on case. A data recorder was attached to the subject's belt. Patients were asked not to shower during the recording period and instructed to record, directly to the device and manually to a diary, the time they spent eating and drinking and their position (upright, supine) during the 24-hour period. If there was any discrepancy, periods logged in the device were modified according to the diary. Time spent eating and drinking was excluded from the analyses of pharyngeal pH recordings. A standardized RYAN composite score was calculated automatically using the software supplied. A RYAN score is a composite pH score for pharyngeal acid exposure calculated from volunteers without reflux problems. A composite pH score was calculated for the pH threshold identified by

TABLE 1. Demographic data and RSI of overall study group and individual groups I, II, and III

	Overall group	Group I	Group II	Group III
Age (years), mean $\pm$ SD	46.0 $\pm$ 13.6	39.3 $\pm$ 12.5	44.3 $\pm$ 11.7	54.4 $\pm$ 12.2
Gender, n				
Male	47	11	19	17
Female	43	19	11	13
RSI, mean $\pm$ SD	10.5 $\pm$ 4.1	8.7 $\pm$ 4.9	9.7 $\pm$ 4.0	13.2 $\pm$ 3.3

RSI = Reflux Symptom Index; SD = standard deviation.

applying the same method used to calculate the composite pH score for esophageal pH monitoring (DeMeester score). The sum of the 3 component scores (percent time below threshold, number of reflux episodes, and duration of the longest episode) equals the pharyngeal composite pH score.²⁵ Patients with pathological RYAN composite scores in the vertical (higher than 9.4) and/or horizontal (higher than 6.8) position were classified as having pathological EER. The number of EER episodes and total percentage of time below pH 5.5 were also assessed.

Statistical analysis

The age, gender, RSI, the severity of EER evaluated using the Restech system and number of previous FESS were compared between group I, group II, and group III. The statistical analysis was performed using Stata 13 software (Stata Corp, College Station, TX). The following statistical tests were used: arithmetic mean, standard deviation, Pearson's chi-squared test, Fisher's exact test, analysis of variance (ANOVA), odds ratio (OR) calculation with 95% confidence intervals, and logistic regression. The statistical tests were assessed on a significance level of 5%.

TABLE 2. Data from oropharyngeal pH monitoring for groups I, II, and III

	Group I	Group II	Group III
Reflux upright, n (% of patients with proved EER)	6/30 (20%)	17/30 (57%)	28/30 (97%)
RYAN score upright (mean $\pm$ SD)	5.3 $\pm$ 10.7	61.3 $\pm$ 103.7	408 $\pm$ 453.8
Reflux supine, n (% of patients with proved EER)	5/30 (17%)	9/30 (30%)	15/30 (50%)
RYAN score supine (mean $\pm$ SD)	3.1 $\pm$ 2.3	5.9 $\pm$ 7.1	18.8 $\pm$ 25.7
Number of episodes (mean $\pm$ SD)	3.0 $\pm$ 3.7	18 $\pm$ 18.7	43.7 $\pm$ 61.5
Percent of time below pH 5.5 (mean $\pm$ SD)	0.2 $\pm$ 0.3	0.9 $\pm$ 1.6	5.2 $\pm$ 11.3

EER = extraesophageal reflux; SD = standard deviation.

Results

A total of 107 consecutive patients who had met the inclusion and exclusion criteria were invited to participate in the study from September 2012 to December 2014. A total of 90 patients (30 in each group) agreed to participate. Enrollment of patients was terminated when all groups consisted of 30 patients. All enrolled patients tolerated the Restech catheter well and completed the 24-hour oropharyngeal pH study. There were no errors associated with oropharyngeal pH monitoring and no missing data. Therefore, all 90 patients were included in further statistical analysis.

Demographic data

Demographic data of the overall study group and individual groups I, II, and III are summarized in Table 1. The overall study group consisted of 47 males (aged 46.7 ± 13.5 years) and 43 females (aged 45.2 ± 13.7 years). There was no difference in age between males and females ($p = 0.594$). Patients in group III were significantly older in comparison with patients in group I and group II ($p < 0.001$). There was no difference in gender between groups ($p = 0.099$) (Table 1).

RSI

RSI was significantly higher in group III when compared with group I and group II ($p < 0.05$); there was no difference between group I and group II (Table 1).

Results of oropharyngeal pH monitoring

Data from oropharyngeal pH monitoring for groups I, II, and III are summarized in Table 2. Pathological EER in the upright position was significantly often present in group III when compared with group I ($p < 0.001$) and group II ($p < 0.004$). Moreover, EER was present in group II significantly often when compared with group I ($p < 0.005$). The average RYAN score in the upright position differed significantly between groups ($p = 0.0001$). The highest average RYAN score was noted in group III and the lowest in group I (Table 2, Fig. 1).

Pathological EER in the supine position was significantly often diagnosed in group III when compared with

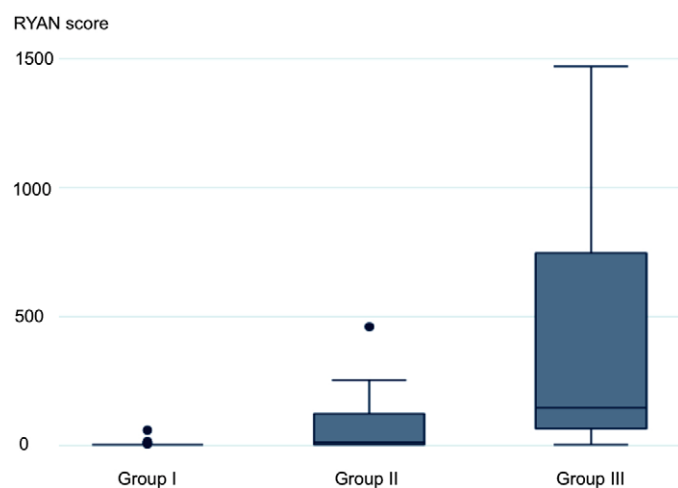


FIGURE 1. Graph showing average upright RYAN score for groups I, II, and III.

group I ($p < 0.008$). No other statistical difference was noted. The average RYAN score in the supine position differed significantly between groups ($p = 0.0042$) as well (Table 2).

Number of EER episodes differed significantly between group I and group II ($p < 0.05$) and between group I and group III ($p < 0.05$). Moreover, the total percentage of time below pH 5.5 differed significantly between group I, group II, and group III ($p = 0.0001$). The longest time under pH 5.5 was recorded in group III, whereas the shortest time under pH 5.5 was recorded in group I (Table 2).

Number of previous FESSs

Altogether, 50% (15/30) of patients from group III had undergone more than 2 prior FESSs within the previous 5 years, whereas only 2 of 30 (6%) and none of 30 (0%) patients, in group II and group I, respectively, had undergone more than 2 prior FESSs. The difference was significant ($p < 0.001$). In the group of patients with >2 prior FESSs within the previous 5 years, the number of patients with pathological EER and average RYAN score was significantly higher when compared with no previous FESS group and the group with 1 to 2 previous FESSs ($p < 0.001$ and $p = 0.0001$, respectively) (Table 3, Fig. 2).

Discussion

EER has recently been cited as a possible risk factor for many respiratory symptoms, signs, and diseases; eg, hoarseness, laryngitis, globus, cough, laryngospasm, bronchial asthma, recurrent and chronic otitis media, and CRS.^{26–29} Of these conditions, the relationship between CRS and EER is the least studied; only a few studies having been conducted within the last decade.^{8–18} These studies have found more hypopharyngeal or nasopharyngeal reflux episodes in patients with refractory CRS and/or early recurrence of nasal polyps after FESS when compared with patients who had no recurrence. The authors conclude that antireflux

TABLE 3. Number of previous FESSs within the last 5 years in groups I, II, and III^a

	No previous FESS	1–2 previous FESSs	>2 previous FESSs
Group I	27	3	0
Group II	13	15	2
Group III	2	13	15
Reflux upright	12/42 (28.6%)	22/31 (71%)	17/17 (100%)
RYAN score upright	15.9 ± 36.8	186 ± 299.8	458 ± 499.6

^aReflux upright and RYAN score upright are listed for groups with different numbers of previous FESSs.

FESS = functional endoscopic sinus surgery.

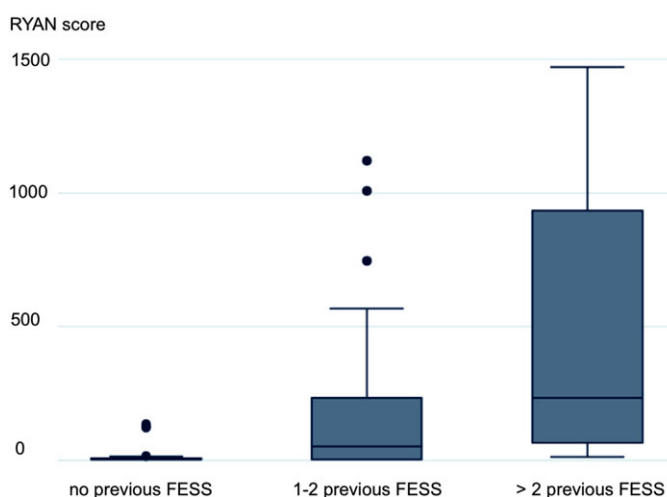


FIGURE 2. Graph showing average upright RYAN score for groups with no previous FESS, 1 to 2 previous FESSs, and >2 previous FESSs.

therapy should be considered in patients with refractory CRS.^{8–13} No other factors that could help us identify patients with CRS and also with EER who are suitable for antireflux therapy have been discussed so far.

Regarding the relationship of bronchial asthma and reflux, asthmatic patients have more gastroesophageal reflux disease and more EER symptoms than the general population. There is not a clear understanding of why this is the case. Consensus exists on the antireflux treatment of patients with bronchial asthma and simultaneous “classical” symptoms of gastroesophageal reflux disease (pyrosis, regurgitation).³⁰ However, empirical PPIs therapy in adults with asthma results only in a small statistically significant improvement in morning peak expiratory flow rate. The magnitude of this improvement is unlikely to be of meaningful clinical significance. Because of many controversies, inconsistent results, and insufficient evidence, the empirical use of PPIs for routine treatment of asthmatic patients with only extraesophageal symptoms is not recommended.^{23,30} As in the case of patients with CRS, there is a need to identify the phenotype of asthmatic patients who would respond to antireflux therapy.^{23,30,31}

EER is considered to be a frequent cofactor of many respiratory symptoms, signs and diseases, including CRS and bronchial asthma. As a result, antireflux therapy, most often using PPIs, has been widely introduced as the recommended treatment for these extraesophageal manifestations. However, treatment of patients with suspected EER using PPIs is often disappointing. This applies not only to patients with CRS, but more generally to patients with most extraesophageal manifestations (dysphonia, reflux, cough, etc.). Most studies attempting to prove the superiority of PPIs over placebos in the treatment of EER have failed.²⁶

Two main reasons are considered as possible reasons for this failure. The first is that EER is not diagnosed properly (often only on the basis of symptoms), and therefore many patients diagnosed as having EER do not really suffer from EER; hence, naturally antireflux therapy will not work. Which is to say that difficulties in treating EER patients arise from the inability to diagnose EER accurately and to select those patients who are suitable candidates for antireflux therapy. In the search for “antireflux therapy responders,” 2 general assumptions can be made. First, there exist some signs (eg, age, gender, body mass index [BMI], specific symptoms, certain characteristics, another diagnosis, etc.) whose presence in a particular patient can predict a better response to antireflux therapy. The second is an assumption regarding pH studies. Generally speaking, if stricter criteria are used for diagnosing pathological EER, a higher positive response rate to the treatment will be achieved.^{29,32}

The second explanation for failure to respond to PPIs may have to do with the fact that pepsin plays the main role in some patients with EER.³³ In these patients, the treatment should be focused not only on the acidity cut-back but also on the reduction of the reflux episodes and minimization of the negative pepsin effect.^{34,35}

The ideal method for diagnosis of EER in patients with CRS and bronchial asthma would be one that could accurately predict their response to antireflux treatment. Unfortunately, such a method does not exist at present. It can only be assumed that patients with more serious symptoms, signs, and/or more severe EER detected by pH monitoring are at higher risk for developing EER-related respiratory disease, and would be potential candidates for antireflux treatment.

In the present study, the hypothesis that patients with simultaneous CRS and bronchial asthma would suffer from the most severe reflux and would therefore be suitable candidates for antireflux therapy was formulated. Patients with different types of CRS were examined for the presence and severity of EER; patients with simultaneous bronchial asthma were enrolled in group III. The results of pH analysis showed that pathological EER was significantly often present in group III when compared with group I and group II in all parameters analyzed (RYAN score in the upright and supine positions, number of EER episodes, total percentage of time below pH 5.5). In almost all (28/30) patients from group III, pathological EER was confirmed, whereas

in group I and group II, EER was confirmed only in 6 of 30 and 17 of 30 patients, respectively. Also of interest is the finding that the average RYAN score in the upright position (408) was many times higher, when compared with the physiological threshold (9.4). On the other hand, patients from group I with CRS without nasal polyps and without bronchial asthma essentially did not suffer from EER. Only in 6 patients from group I was a very little reflux detected, and the average RYAN score for group I was even below the physiological threshold (5.3). The results confirmed the study hypothesis that patients with CRS and simultaneous bronchial asthma suffer from significant EER. Besides, it was also revealed that patients with CRS without nasal polyps rarely suffer from EER.

Analysis of demographic data showed that patients from group III were significantly older (54 years), when compared with group I and group II (39 and 44 years, respectively). This is consistent with the fact that increasing age has been confirmed as a risk factor for new onset of gastroesophageal reflux disease.³⁶

Symptoms of EER are heterogeneous, nonspecific, and of very limited diagnostic value. Therefore, the RSI was developed by Belafsky et al.²⁴ Use of the RSI for the diagnosis of EER in patients with CRS has not been reported so far. In the present study, significantly higher RSI (13.2) was noted in patients with CRS and simultaneous bronchial asthma when compared with other groups. However, the RSI was only slightly higher than 13, which is the threshold given by Belafsky et al.²⁴ Moreover, when considering standard deviations, the RSI goes below the threshold established and accordingly does not identify patients with EER. Therefore, we can only conclude that RSI might be helpful in the diagnosis of EER in patients with CRS.

Altogether, 50% (15/30) of patients from group III had undergone more than 2 previous FESS within the previous 5 years, while only 2 of 30 (6%) and none of 30 (0%) patients, in group II and group I, respectively, had undergone more than 2 prior FESSs. This means that CRS in group III was not controlled well. This is in accordance with the results of previous studies, which compared the severity of EER in patients with refractory CRS and/or early recurrence of nasal polyposis after FESS with patients with well controlled CRS. These studies found more hypopharyngeal or nasopharyngeal reflux episodes in patients with early recurrence of nasal polyposis after FESS.^{8–13}

Although important, diagnosis of EER in patients with CRS is not easy. Currently, 24-hour dual-probe esophageal pH monitoring or impedance is considered the best diagnostic method for EER. However, the position of the sensor, which is placed in the esophagus or hypopharynx, does not reflect the amount of reflux content that reaches the nasopharynx. Therefore, a diagnostic method that is able to detect pH in the oropharynx or nasopharynx would seem to be indicated for the diagnosis of EER in patients with CRS.

Twenty-four-hour measuring of oropharyngeal pH with the Restech system has become widespread within the

last decade. This method is less invasive and much better tolerated.^{25,37} However, there are some disadvantages of this method as well. In particular, the absence of a distal sensor, which means that it is necessary to rely on data about meal periods and the position of the patient as recorded by the patient. Nevertheless, the majority of studies comparing esophageal and oropharyngeal pH measurement (simultaneous monitoring in 1 patient) have established good reciprocal correlation between these 2 methods.^{25,38} In the present study, the oropharyngeal Restech catheter was tolerated well by all patients and there were no errors or missing data. Therefore, 24-hour oropharyngeal pH monitoring seems to be a good diagnostic tool for making the diagnosis of EER in patients with CRS.

One limitation of this study should be mentioned. Group III had significantly older patients than group I or group II. This can be seen in 2 ways. The first explanation is that older patients suffer often from reflux and their reflux is more severe and consequently it worsens CRS and

bronchial asthma. And therefore they need more surgeries. The second explanation might be that patients in group III are older and need more surgeries because they suffer from CRS longer. We tried to eliminate this potential bias when the number of previous FESSs was ascertained within the last 5 years before the study. The ongoing studies should take into account this potential weakness in their methodology.

Conclusion

According to the results of the present study it can be concluded that patients with CRS with nasal polyps and simultaneous bronchial asthma suffer from significant EER. Patients suffering from CRS with nasal polyps and simultaneous bronchial asthma who have had more than 2 prior surgeries for CRS seem to be the most suitable candidates for antireflux treatment. However, the effect of antireflux therapy in these particular patients has to be confirmed in further studies. 

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