Gastro-oesophageal reflux in patients with chronic rhinosinusitis investigated with multichannel impedance - pH monitoring*

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Rhinology 55: 0-0, 2017
https://doi.org/10.4193/Rhino16.275

***Received for publication:**
September 23, 2016
Accepted: November 23, 2016

Abstract

Introduction: The pathophysiology of chronic rhinosinusitis (CRS) is unclear. It has been discussed for decades whether gastro-oesophageal reflux (GOR) may be a contributing factor for some patients. The aim of the present study was to evaluate the level of GOR in an unselected group of patients with CRS using multichannel impedance-pH monitoring.

Methods: Consecutive patients with CRS diagnosed using the EPOS2012 criteria, completed questionnaires on GOR symptoms and were offered 24-h multichannel intraluminal impedance (MII)-pH monitoring. The results were compared with a group of healthy controls.

Results: Forty-six patients completed MII-pH-monitoring and were compared with 45 control subjects, with comparable age and gender distributions. The median number of reflux episodes in the patients was 56.5 compared with 33 in controls, while, the numbers of proximal reflux episodes was 27.5 versus 3, respectively. Thirty nine patients had abnormal pH-impedance recordings compared with five controls.

Conclusion: The CRS patients had significantly higher incidences of gastro-oesophageal reflux compared with asymptomatic controls. The results of this study suggest that GOR may be a causative or contributing factor of CRS.

Key words: chronic rhinosinusitis, gastro-oesophageal reflux, 24-h multichannel intraluminal impedance-pH- monitoring

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Introduction

Chronic rhinosinusitis (CRS) is a disease with multifactorial and partly unknown aetiology. It is characterized by inflammation of the mucosa of the nasal and paranasal sinuses lasting for at least 12 weeks. It is a highly prevalent disease, affecting up to 15 % of the adult population, with a negative impact on quality of life and health in general [(1)]. For medical doctors, these patients are a challenge, as they frequently fail to respond to conventional medical and surgical treatments. Therefore, it is of major interest to understand more about the pathophysiology of the disease.

Gastro-oesophageal reflux is a physiological phenomenon, but may cause symptoms in a subgroup of adults and children. Gastro-oesophageal reflux disease (GORD) is diagnosed if GOR causes significant symptoms or mucosal complications [(2)]. It may present with a wide spectrum of symptoms and can be divided into oesophageal syndromes and extra-oesophageal syndromes, depending on the presumed origin of symptoms. Oesophageal syndrome is further divided into erosive reflux disease or non-erosive oesophageal reflux disease, depending on whether there is visible damage to the oesophageal mucosa or

not. Extra-oesophageal syndrome can occur concomitantly with typical GORD or without, and when symptoms from oesophageal syndrome occur without classical symptoms, the diagnosis of reflux as a contributing factor may be delayed. About 20 - 40 % of the Western population demonstrate symptoms possibly related to reflux, involving typical GORD symptoms alone or in combination with oesophageal syndrome [3]. When defined as at least weekly symptoms of heartburn and/ or acid regurgitation, the prevalence of GORD is 10-20 % in Western countries and 2.5-3.8 % in Asia [4]. The lack of standardized diagnostic criteria may be one reason for the differences in prevalence.

It has been discussed for decades whether GORD can be a contributing factor for some CRS-patients [5]. Two different pathophysiological mechanisms have been proposed to explain how GORD might contribute to airway manifestations. One theory is that there is a direct cytotoxic effect of refluxate on the respiratory mucosa. The other suggests an indirect mechanism involving a neural reflex from the oesophagus to the upper airways via the autonomic nervous system [6, 7]. According to The European Position Paper on Rhinosinusitis and Nasal Polyps 2012 (EPOS2012) there is insufficient evidence for a causal relationship between GORD and CRS [1]. Nevertheless, there is still debate over whether there is an association or not [8]. Patients with GORD have a higher 20-item Sino Nasal Outcome Test (SNOT-20) score than control subjects, indicating that GORD patients have a reduced sino-nasal quality of life [9].

Thus, it is important to verify if there is an association between GORD and CRS to optimize the investigation, treatment and follow up of patients with refractory CRS. Verifying a causal relationship between GOR and CRS may lead to new therapeutic strategies. From this perspective proper strategies for diagnosing GORD are mandatory. Impedance monitoring of the oesophagus combined with pH recordings is a novel diagnostic approach. It is the most sensitive method for detection and characterization of GORD and currently the diagnostic procedure of choice. Twenty-four hour multichannel intraluminal impedance (MII)-pH monitoring can detect both acid and non-acid reflux, and is able to determine the proximal extent of the refluxate [10-12]. The aim of the present study was to evaluate the prevalence of abnormal gastro-oesophageal reflux patterns in patients with CRS using ambulatory 24-h impedance and pH-monitoring and compare the result with healthy controls.

Materials and methods

Patients and controls

In this prospective case controlled study, consecutive patients above 18 years of age who were referred to the ENT department, Stavanger University Hospital and diagnosed with CRS according to the EPOS 2012 criteria [1], were invited to participate. Diagnosed and treated GORD was an exclusion criterion, but not prior sinus surgery. In all, 21 women and 25 men were included with a mean age of 48.4 years, ranging from 23 to 73. The patients completed 24-h impedance-pH monitoring, with reliable recordings for 18-25 hours (Table 1).

Table 1. Demographic data for the 46 patients with chronic rhinosinusitis (CRS) and 45 healthy controls.

	CRS Patients	Control subjects
Mean age, years	48.4	46.3
>50 years, n	20	21
>60 years, n	10	7
Range, years	23-73	18-78
Sex, Woman/ Men	21/25	22/23
Mean BMI* (Confidence Interval)	25.0 (23.8 , 26.3)	23.9 (22.9 , 24.8)

* BMI= Body Mass Index

Our results were compared with healthy subjects in an existing database on 24-h impedance pH-monitoring [10]. This dataset was partly used as a control group, as well as to define the upper limit of normal for the various measurement variables, and as a reference for normal or pathological pH-impedance recordings in CRS. In the control population, there were 22 women and 23 men, mean age was 46.3 years, ranging from 18 to 78 (Table 1).

24-h impedance-pH monitoring

The study was performed on an outpatient basis, and all patients were informed and examined by the same investigator. The participants had an overnight fast before undergoing oesophageal manometry to localize the level of the upper and lower oesophageal sphincters (UOS/LOS). The mean LOS resting pressure and the motility pattern of the oesophagus were assessed. The impedance pH-catheter (ZAN-BG-44, Sandhill Scientific, Inc.; Highland Ranch, CO, USA) was positioned transnasally into the oesophagus, with the proximal pH-electrode situated 5 cm proximal to the upper margin of the LOS. The catheter contained two pH-electrodes, one at 5 cm above the LOS and one in the proximal stomach. Impedance electrodes were located at 2, 4, 6, 8, 10, 14, 16 and 18 cm above the LOS measuring all levels in the oesophagus (Figure 1). In advance of each measurement, the data recorder and probe were calibrated using pH 4.0 and pH 7.0 buffer solutions.

The principle of impedance monitoring is that the presence of liquid in the oesophagus leads to a drop in impedance. In case of gastro-oesophageal reflux, a 50 % drop in impedance from baseline will be seen as a retrograde move along the catheter. The participants were encouraged to maintain their normal activities and take meals as usual during the recording. They were

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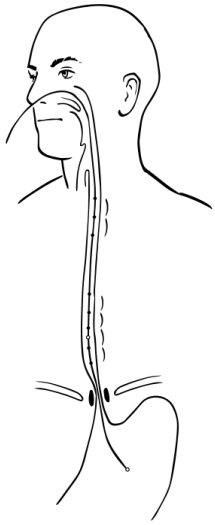

Figure 1. Catheter placement for monitoring gastro-oesophageal reflux with multichannel intraluminal impedance. Impedance is measured between electrodes located at 2, 4, 6, 8, 10, 14, 16 and 18 cm above LOS.

asked not to drink beverages with a pH <4 between meals. The patients used the data logger (Sleuth, Sandhill Scientific Inc.) to record meal times, changes in posture and the occurrence of the following specific symptoms: regurgitation, chest pain, cough and the need to clear the throat. We scored the symptom-reflux time association with the Symptom Index (SI) [13] and Symptom Association Probability (SAP) [14].

The number of reflux episodes of the oesophagus as well as the number of reflux episodes with proximal extent, defined as reaching the impedance electrodes 15 cm proximal to the LOS, were recorded. Bolus exposure was calculated as the % of total recorded time, and all variables were separated into reflux when recumbent or upright, as well as acid (pH<4) or non-acid (pH>4) reflux. As GOR is not normally distributed, all exposure variables were calculated as median values with an inter-quartile range (IQR). The analysis was performed with BioView version 5.4.3 (Sandhill Scientific Inc.). The analyses were done automatically with the Autoscan function of BioView, and then hand edited by two investigators.

The controls underwent a similar study protocol for 24-h oesophageal impedance-pH monitoring [10].

Questionnaires

Impedance pH-monitoring parameters were correlated to symptom severity of CRS using symptom scores from Visual Analogue Scales (VAS CRS) and the SNOT-20. The VAS CRS is a psychometric response scale used to measure subjective characteristics of sino-nasal symptoms [1]. The SNOT-20 is a validated, self-administered, quality of life instrument specific for patients with symptoms of rhinosinusitis [15].

The Gastro-esophageal Reflux Disease Questionnaire (GerdQ) [16] was used to record classical symptoms of GORD. The GerdQ is a six item validated, self-administered questionnaire.

Statistical analysis

The data were not normally distributed, therefore the Mann-Whitney U test was used to test for differences between patients and controls, and median and interquartile range (IQR) are reported as descriptive statistics. A p value less than 0.05 was considered statistically significant. The analyses were done using SPSS ver. 23 (Statistical Package for Social Sciences, Chicago, IL, USA).

Based on a sample size calculation prior to the study, we needed at least 45 patients to discover a difference in bolus exposure between a normal population and a study population. This sample size calculation was based on that we wanted to have 90 % power to discover a mean difference in bolus exposure time of at least 0.7 with a two-sided test and of 5 % significance level.

Results

Sixty-five patients fulfilled the inclusion criteria and were invited to participate. Of these, 50 patients accepted and provided signed informed consent. Patients who declined to participate mostly cited fear of the procedures and/or a long travelling distance to the hospital as reasons, and GORD had been diagnosed in three of those patients. Four participants received treatment with a proton pump inhibitor (PPI) for GORD at the time of MII, and were excluded from analysis. Another two participants had previously been treated for suspected reflux, without any classical symptoms at present. In total 46 patients were included.

24-h impedance pH-monitoring

Technically valid recordings lasting >18 h were made for all participants. In the patient group, we found a median of 56.5 reflux episodes per monitoring, compared with 33 in the control group (p<0.0005, Table 2 and Figure 2a). With an upper limit of normal of 65.6 (upper 95% percentile of control group), 17 patients (37%) had an abnormal total number of reflux episodes. The majority of reflux episodes (52.2) occurred in an upright position. The median number of reflux episodes reaching the proximal oesophagus was 27.5 in patients vs. 3 in controls (p>0.0005), with as many as 34 patients (73.9%) with an abnormal number of proximal reflux episodes (Table 2 and Figure 2b). In the patient group, the median reflux bolus exposure was significantly higher than in the control population, 1.7 % (IQR 1.0- 2.7) of the time vs. 0.9 % (IQR 0.5 -1.6) (p=0.001, Table 2 and Figure 2c). Based on normal values from the control population, nine patients (26.1%) had abnormal bolus exposure. Most of the bolus exposure was detected when upright, only two patients had abnormal bolus exposure when recumbent.

When analysed as traditional pH- monitoring, we found distal oesophageal acid exposure calculated as fraction time with

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Table 2. Results from 24-h impedance pH-monitoring of patients with chronic rhinosinusitis (CRS) and controls

	CRS patients Median (IQR**)	Control subjects	Mann-Whitney U-test	Upper limit of normal (>95 % percentile)	No. patients above normal (%)	No. controls above normal (%)
Number of reflux episodes N (IQR)						
Total	56.5 (33.8-78.8)	33 (16.5-47.5)	p<0.0005	65.6	17 (37.1)	2 (4.4)
Upright	52.5 (33.5- 71.0)	28 (14.5- 43.0)	p<0.0005	60.7	19 (41.3)	1 (2.2)
Supine	2.0 (1.0- 5.3)	2.0 (0.5- 3.5)	p=0.163	10.1	6 (13.0)	2 (4.4)
Non-acidic	19 (10.0- 34.0)	8 (3.0- 13.5)*	p<0.0005	27.5	14 (30.4)	2 (4.4)
Acidic	28.5 (19.8-52)	22 (10.5- 35)	p=0.020	46.2	13 (28.3)	2 (4.4)
Proximal extent						
Total	27.5 (14.8- 46.5)	3 (1-7)	p<0.0005	15.5	34 (73.9)	2 (4.4)
Upright	27 (14.8- 44.0)					
Supine	1 (0.0- 3.0)					
24-h bolus exposure % time (IQR)						
Total time	1.7 (1.0-2.7)	0.9 (0.5- 1.6)	p=0.001	2.6	9 (20.0)	2 (4.4)
Upright	2.4 (1.5-4.0)	1.3 (0.7- 2.3)	p<0.0005	4.3	6 (13.0)	1 (2.2)
Supine	0.2 (0.0-0.5)	0.1 (0.0-0.2)	p=0.099	1.9	1 (2.1)	2 (4.4)
Non-acidic	1.1 (0.4- 2.2)					
Acidic	0.5 (0.2- 0.8)					
Oesophageal acid exposure % time pH<4 (IQR)						
Total time	2.4 (0.9- 5.8)	1.4 (0. 6- 2.7)	p=0.029	7.3	7(15.2)	2 (4.4)
Upright	3.2 (1.1-8.0)	2.0 (0.6-4.1)	p=0.031	7.1	12 (26.1)	1 (2.2)
Supine	0.1 (0.0-0.9)	0.0 (0.0-0.4)	p=0.237	10.5	1 (2.2)	2 (4.4)
Number of episodes >5 min	0.0 (0.0- 3.1)					

*combination of weakly acidic and weakly alkaline, **IQR= Interquartile range

pH<4.0 to be 2.4% in CRS patients, compared with 1.4 % in controls (p=0.029, Table 2). Based on an upper limit of normal of 7.3% in the control group, 7 patients (15.2%) had abnormal acid exposure in the oesophagus. When looking at impedance we found that 35 patients had pathological recordings due to more reflux episodes, bolus exposure or the proximal extent of the refluxate.

Age and gender

There were no significant differences between the patients aged >45 years vs. < 45 regarding reflux episodes bolus exposure and the proximal extent of refluxate (p=0.75, p=0.37 and p=0.58 respectively). The total number of reflux episodes and bolus exposure were higher in men than in women both in the study group (p=0.002 and p=0.004, respectively) and control group (p=0.002 and p=0.002 respectively).The number of proximal reflux episodes in the patient group was higher in men than in women (p=0.001), but was not significantly different in the control group. There were significant differences in the total number of reflux episodes, bolus exposure and proximal extent of the refluxate between males in the study group and males in the control group (p<0.0001, p=0.005, and p<0.0001 respectively), and similarly for females (p=0.006, p=0.008 and p<0.0001, respectively).

Symptoms and questionnaires

Forty-three of the 46 patients reported one or more of the four specific symptoms recorded and used for calculating the SI and SAP (Table 3).

There was no correlation between GerdQ total score and MII-pH monitoring, in the total number of reflux episodes (r=0.17, p=0.28), number of proximal reflux episodes (r= 0.12, p=0.44) nor bolus exposure (r= 0.10, p=0.52) in the patient group.

We did not find any correlation between the number of reflux episodes with proximal extent or oesophageal bolus exposure, and the VAS CRS or the SNOT-20 (data not shown). The median total SNOT-20 score in the study population was 27 (IQR 18- 43).

Body Mass Index (BMI)

There was a small difference between BMI in the two groups,

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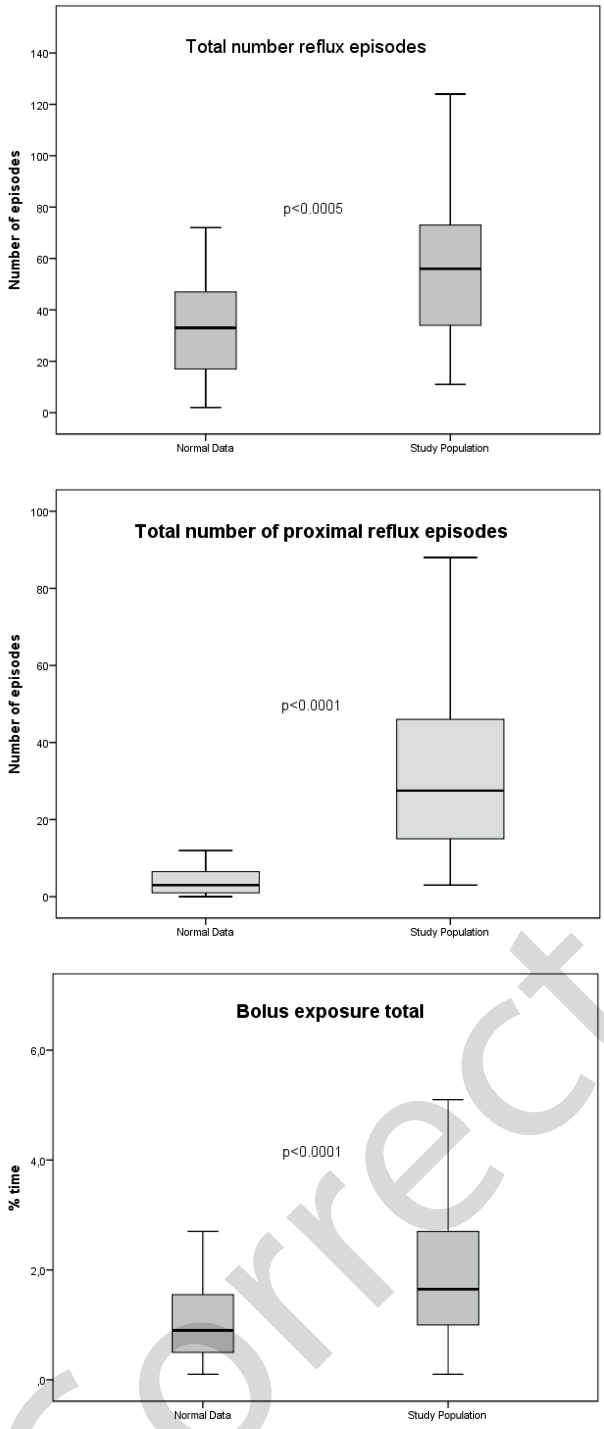

Figure 2. (A)Total number of gastro-oesophageal reflux episodes during 24- h impedance pH-monitoring in 46 patients with chronic rhinosinusitis compared with 45 healthy control subjects. The box represents the median and interquartile range, and the whiskers indicate the range. (B) Total number of proximal reflux episodes over 24- h in 46 patients with chronic rhinosinusitis compared with 45 healthy controls. The box represents the median and interquartile range, and the whiskers indicate the range. (C) Bolus exposure (% of recorded time) over 24- h in 46 patients with chronic rhinosinusitis compared with 45 healthy controls. The box represents the median and interquartile range, and the whiskers indicate the range.

with higher BMI in the patient group, but the difference was not significant (p=0.13). There was no correlation between BMI and MII-pH in the patient group regarding total number of reflux episodes (r=0.22, p=0.17), total number of proximal reflux episodes (r=0.15, p=0.39) or bolus exposure (r=0.08, p=0.64) and no correlation between BMI and the total number of reflux episodes (r=0.24, p=0.11) in the control group. There was a weak correlation between BMI and MII-pH, regarding total number of proximal reflux episodes (r=0.33, p=0.03) and bolus exposure (r=0.34, p=0.02) in the control group.

Discussion

The main findings in this study were that patients with CRS had more gastro-oesophageal reflux as well as proximal reflux, than healthy controls. The CRS patients also had significantly more bolus exposure in both the upright and supine positions. There were significantly higher numbers of acid and non-acid reflux episodes in patients than controls. Oesophageal acid exposure was also significantly different between patients and controls, but fewer patients had abnormal values, and the group differences were much less pronounced. To the best of our knowledge, this is the first study using MII-pH monitoring – the method of choice - to assess the reflux incidence in CRS patients.

With two prevalent disorders, we expected overlap between entities in the same patients, and indeed a subgroup of our CRS patients did have some oesophageal symptoms of reflux. Still, reflux episodes extending to the upper third of the oesophagus were not numerous in the controls, and it is not a common finding in patients with oesophageal syndromes of GORD in general. Gastro-oesophageal reflux is thought to cause extra-oesophageal manifestations either via a direct toxic effect on mucosal surfaces, or indirectly via neural pathways. It may be speculated that the presence of proximal reflux in the study population supports the presence of the direct-toxic-effect mechanism from refluxate to the airway mucosa in patients with CRS. Generally, PPIs have a poor effect on CRS when reflux is the suspected underlying mechanism. This may be explained by the non-acid character of the refluxate in cases with CRS, as was demonstrated in this study.

The present study population had CRS according to the EPOS2012 criteria (1). This includes having two or more of the typical symptoms: nasal blockage/ obstruction/ congestion, nasal discharge, facial pain/ pressure, and reduced/ lost sense of smell. One of the symptoms must be nasal obstruction or nasal discharge. The symptoms lasted for more than 12 weeks. The inflammation of nose and paranasal sinuses was verified by either mucosal changes in the ostiomeatal complex and/ or sinuses on CT scans or endoscopic signs of nasal polyps, mucopurulent discharge or mucosal oedema/ obstruction of the ostiomeatal complex.

Diagnosing extra-oesophageal syndromes can be difficult.

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Table 1. Number of patients having symptoms, a positive Symptom Index, and a positive Symptom Association Probability.

Symptom	Chest pain	Cough	Need to clear the throat	Regurgitation
Occurrence, N of patients (%)	11 (24 %)	38 (83 %)	17 (37 %)	21 (46 %)
Positive SI*, >50 and at least 3 registrations (%)	2 (4 %)	9 (20 %)	4 (9 %)	8 (17 %)
Positive SAP** >0.95 (%)	3 (7 %)	7 (15 %)	7 (15 %)	9 (20 %)
Positive SI* or SAP** (%)	3 (7 %)	11 (24 %)	11 (24 %)	9 (20 %)

*SI= Symptom Index **SAP= Symptom Association Probability

Questionnaires including the Reflux Disease Questionnaire (RDQ) [17] and GerdQ [16] are based on medical history, and will only include patients with typical oesophageal symptoms. Thus, they are not sensitive for detecting patients without heartburn or regurgitation. Upper gastro-intestinal endoscopy has high specificity in diagnosing GORD; however, the sensitivity is low as it will only include patients who have complications with oesophageal lesions. In the present study, it was important to find the prevalence of all phenotypes of GORD. Thus, we needed a diagnostic instrument with the capacity to detect the disorder even in the absence of classical symptoms and damage of the oesophageal mucosa. For many years, 24-h pH-recordings of the oesophagus, were the gold standard for diagnosing GORD. However, this does not detect nonacid reflux, and the rate of false negatives and false positives might be as high as 30% [18].

The 24-h MII- pH monitoring, detects and quantifies abnormal gastro-oesophageal reflux irrespective of symptoms or mucosal changes by identifying retrograde fluid movement in the oesophagus. It also supplies data on the proximal extent of the refluxate. Thus, this technique is more sensitive for studying the pathogenesis and diagnosing the various phenotypes of GORD and its proximal extent than other alternatives [3, 10-12]. The superiority of pH impedance in reflux investigation, and the inferiority of other investigational strategies are supported by the present study. We did not find any correlation between the GerdQ and MII- recordings, and we found a low SI Score and low SAP. This illustrates the insufficiency of symptoms as a diagnostic criterion for reflux. Prior studies of associations between GOR and CRS used pH-monitoring to determine the presence or absence of reflux [8]. Accordingly, individuals with non-acid reflux were excluded. This may explain the lack of concordance between the present and previous investigations for associations between the two entities.

The reliability of automatic analyses and the similarity to manual editing have been debated. A software program must be able to distinguish between impedance changes due to real reflux and changes due to non-reflux phenomena such as swallowing or random changes in intra-oesophageal impedance. The MII-pH data in the present study were analysed both automatically and manually and there were only small differences between the two analyses. This corresponds with previous investigations [19].The control subject population did not have typical or atypical symptoms of GORD. Among the CRS patients two had a history of medically treated reflux. It could be a source of error if patients included in the present study had GORD at a higher prevalence than CRS patients in general. The two patients had pathological pH-impedance monitoring.

The total number of reflux episodes was higher in men than in women, both in the study group and in the control group. Thus, the higher male/female ratio in the study group (25/21) compared with the control group (23/22) might be a potential source of error. To address this, we compared the data from males and females in the study group and control group separately and found no significant differences between genders. There is no good documentation in the literature that supports such a difference in the population.

It has been discussed whether or not gastro-oesophageal reflux varies with age or not. In our patients, we did not find a significant difference between those older or younger than 45 years neither regarding number of bolus exposure nor bolus exposure. Our patients had the same range in age as the controls. Thus, age was not a determining factor for the results in the present study. We did not find any correlation between the number of proximal extent episodes or the percent bolus exposure and the VAS CRS or SNOT-20. This implies that those with of the most severe reflux diagnosed with impedance are not necessarily those having the worst CRS symptoms. The BMI is positively associated with symptoms of GORD, and even a moderate weight gain among subjects with normal weights may cause symptom exacerbation [20]. Although the difference between BMI in the patients and the controls was not significant, we also checked for a correlation between BMI and pH-MII parameters, to exclude the risk of BMI introducing a bias in our study. There was no correlation in the study population and only a very weak correlation among the healthy controls.

According to the Montréal consensus, certain airway manifestations are well documented as associated with GORD, whereas others are more speculative, including CRS. Documented associations include GORD as a common cause of chronic cough [21], asthma and laryngitis [2], dental erosions [21,22], and otitis media with effusion [23, 24]. The present study supports a causative association between CRS and GORD as there is an increased coexistence between the two and we identify pathophysiological mechanisms linking them to each other.

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Conclusion

We found that CRS patients had a significantly higher prevalence of reflux, measured as a higher number of reflux episodes in the oesophagus and higher number of proximal reflux episodes compared with healthy subjects. Accordingly, this study supports previous investigations suggesting that gastro-oesophageal reflux can be a causative or contributing factor in a subset of patients with CRS.

Acknowledgement

The authors acknowledge Frank Zerbib, PhD for contributing the control material and critically revising the manuscript. Jorunn Totland Strøm at the Department of Medicine, Stavanger University Hospital is acknowledged for excellent assistance and collaboration in performing the monitoring of the patients. Ingvild Dalen, PhD is thanked for providing valuable advice on the statistical analysis. We also thank all patients who participated in the study.

Authorship contribution

EJK, JGH and SKS designed the study. EJK collected the data with assistance from TG. EJK and JGH analysed and interpreted the data. EJK wrote the paper with assistance from all the authors.

Conflict of interest

There is no conflict of interest to report.

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