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Esophageal Dysfunction and Outcome in Patients with Gastroesophageal Reflux-Induced Chronic Cough

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1. Abstract

1.1. Objectives

This study aims to investigate changes in esophageal function in patients with gastroesophageal reflux-induced chronic cough (GERC) evaluated by high-resolution esophageal manometry (HRM).

1.2. Methods

51 patients with GERC, 86 cough patients with non-GERC and 41 patients with cough-free gastroesophageal reflux disease (GERD) were recruited in the retrospective study. General information, cough threshold C2 and C5 to inhaled capsaicin, variables of HRM and esophageal impedance-pH monitoring were reviewed and compared across the three groups.

1.3. Results

C2 and C5 were significantly lower in GERC and non-GERC groups than in cough-free GERD group ($P<0.05$). GERC group had a reduced lower esophageal sphincter pressure, lower distal contractile integral and proportion of normal contractions, but a higher break length, proportion of failed contractions, and proportion of large breaks than non-GERC group. However, there variables were similar between GERC and cough-free GERD groups. Lower esophageal sphincter pressure was lower in patients with non-acid than those with acid GERC (14.20 mmHg vs 23.53 mmHg, $P=0.022$), and intensive anti-reflux therapy was more frequently required in patients with non-acid GERC ($\chi^2=4.813$, $P=0.028$), who also presented with an increase in total reflux episodes and non-acid reflux episode. GERC patients with decreased distal contractile integral had higher daytime cough symptom scores, lower C5, and higher symptom association probability than those with normal distal contractile integral.

1.4. Conclusion

GERC has similar esophageal dysfunction to GERD but with cough hypersensitivity related to its pathogenesis and antireflux outcome.

2. Introduction

Gastroesophageal reflux-induced chronic cough (GERC) is a specific gastroesophageal reflux disease (GERD) with cough as the sole or predominant symptom, and a common cause of chronic cough [1]. Abnormal esophageal structure and function are potentially important factors for GERC pathogenesis and therapeutic efficacy of antireflux drugs [2]. High resolution manometry (HRM) can describe esophageal anatomy and measure esophageal function of peristalsis, in a more accurate way than traditional esophageal manometry does, and now is the most useful technique of esophageal manometry available [3]. In addition to locate the position of the lower esophageal sphincter prior to the placement of esophageal impedance probes combined with pH electrode in esophageal impedance-pH monitoring, HRM is also widely employed for the diagnosis and evaluation of esophageal motility disorders, particularly for the evalua-

tion of esophageal motility before antireflux surgery and after failure to antireflux medicinal treatment. Although there are several reports regarding the esophageal dysfunction evaluated by HRM in patients with chronic cough [4-5], how these changes in esophageal motility are related to GERC remains unclear. In the present study, we investigated the abnormal esophageal pathophysiology indicated by HRM variable in the patient with GERC in a retrospective clinical study.

3. Subjects and Methods

3.1. Patients

The patients referred to our respiratory clinic and recorded in the database of clinical research for chronic cough between August 2018 and January 2020 were screened and recruited into the study. The etiologies of chronic cough was definitively established in all patients according to the diagnostic algorithyn recommended in the guidelines for the management of chronic cough (Chinese version 2015) [1]. Inclusion criteria were that patients with chronic cough who had undergone multi-channel intraluminal impedance combined with pH monitoring (MII-pH) as well as HRM examination. Exclusion criteria included those with incomplete data of follow-up and with multiple etiologies for their chronic cough. Then, the patients with chronic cough were divided into GERC and non-GERC groups based on their causes of chronic cough, while patients with cough-free GERD were designated as the control group. GERC was diagnosed when the patients presented with 1) chronic cough, with or without typical reflux-associated symptoms such as regurgitation and heartburn; 2) MII-pH revealed anyone of the followings: acid exposure time (AET) > 6%, symptom association probability (SAP) ≥ 95% and total reflux episodes > 80/24 h [3]; 3) cough disappeared or obviously improved in response to antireflux therapies including standard regimen (omeprazole 20 mg, twice a day plus domperidone 10 mg, three times a day) or intensive regimens (double dose of omeprazole or combined with neuromodulators such as gabapentin and baclofen) [6]. Patients with AET > 6% or acid SAP ≥ 95% were diagnosed with acid GERC, and those with non-acid SAP ≥ 95% or significant increase in non-acid reflux events was diagnosed with non-acid GERC [6-8]. Non-GERC group consisted of patients with causes of chronic cough other than GERC. Cough-free GERD was diagnosed as the same as GERC, but without cough symptom.

3.2. Clinical Investigations

HRM was conducted using a Solar GI system (MMS, Netherlands). On the testing day, the patients came to our esophageal laboratory after one week of discontinuance of proton pump inhibitors and other medications that effect esophageal motility and an overnight fast. Patients were asked to keep in the supine position, then the manometry catheter with pre-**calibration** was transnasally inserted into the esophagus with the patients` cooperation of swallowing movements, until two high-pressure bands, representing the upper and lower esophageal sphincters respectively, were visible on the topography. The manometry catheter was then fixed in the nose and measurement initiated after 1–2 min of quiet breathing. The resting pressures of the upper and lower esophageal sphincters were measured after a 30-s non-swallowing period in a resting state for 20 s. Then, esophageal motility was measured. Subjects were fed 5 ml of physiological saline to swallow each time for a total of 10 times, with an interval of at least 30 s between swallows, to ensure that the esophageal pressure returned to the resting pressure. If two or more swallows occurred after one feeding of physiological saline, the measurement was considered invalid. During the procedure, a specific computerized software for HRM was used to collect, display and analyze the data, and to identify and record the depth of the inserted catheter, the position and pressure of the upper and lower esophageal sphincters; contractile deceleration point (CDP); length, amplitude and duration of peristaltic contraction of the distal esophagus; break and size of esophageal peristalsis; and to calculate the 4-s integrated relaxation pressure (IRP4s), distal contractile integral (DCI) and distal latency (DL), where peristaltic break > 5 cm was defined as a large break [3]. MII-pH was performed as described previously [8]. Just after the esophageal HRM, a 2.1-mm diameter combined MII-pH catheter assembly containing six impedance electrodes (K6011-E10632, Unisensor, Switzerland) and an antimony pH electrode (819100, Medical Measurement System B.V., Netherlands) was inserted into the esophagus and positioned with impedance electrodes at 3, 5, 7, 9, 15 and 17 cm above the lower esophageal sphincter, and pH electrode 5 cm above the lower esophageal sphincter. Prior to the procedure, the pH electrodes were calibrated using pH 4.0 and pH 7.0 buffer solutions. The catheter assembly was connected to a portable data logger (Ohmega, Medical Measurement System B.V. Netherlands) that collects the data with 50 Hz frequency over 24h. The patients were instructed to keep paper diaries, corroborated with event markers, to record the timing of the start and end of meals, changes in position and symptoms. Using specific software (Database soft, 8.7 version, Medical Measurement System B.V., Netherlands), the data were automatically analyzed but manually reviewed for reflux episodes, which are classified as liquid, gas and mixed reflux, or acidic (pH<4.0) and non-acidic comprizing weakly acidic (pH 4.0-7.0) and weakly alkaline reflux (pH >7.0). Combined with cough time and number recorded on diary cards, symptom association probability (SAP) for acid and non-acid reflux was calculated to establish the temporal association between cough and reflux. Acid exposure time (AET) was used as a global measure of esophageal acid exposure. Abnormal reflux was defined as AET > 6% and/or SAP for acid and nonacid reflux ≥95%. Cough sensitivity to inhaled capsaicin was tested according to the method established in our laboratory [9-10]. Cough threshold was defined as the lowest concentration of capsaicin required for the induction of ≥2 (C2) and ≥5 coughs (C5), and was used as an indicator of cough sensitivity [6].

3.3. Statistical Analysis

Data with normal distribution were expressed as mean ±SD, or as median (25%-75% quartile) if skewed distribution. Cough threshold

C2 and C5 were log transformed to normalize the data and expressed as geometric mean ± SD. Differences in gender distribution among the three groups were analyzed using chi-square test. The comparisons of age and variables reflecting esophageal function across the three groups and between two groups were undertaken using one way analysis of variance (ANOVA) followed by Newman-Keuls test (for normal distribution data) or Kruskal–Wallis test followed by Mann–Whitney U test (for skew distribution data). SPSS 21.0 Software (SPSS Inc, Chicago, IL, USA) was used for statistical calculation. A P-value of <0.05 was accepted as statistically significant.

4. Results

4.1. General Information

Searching the database of clinical research for chronic cough revealed a total of 178 patients who met the inclusion criteria during the study period. After excluding 35 patients who were lost to follow-up, 4 patients with chronic cough of multiple etiologies and 2 patients with incomplete data, 137 patients were finally enrolled, including 51 patients with GERC and 86 patients with non-GERC respectively (Table 1). GERC group comprised 20 cases of acid GERC and 31 cases of non-acid GERC, while non-GERC group included 15 cases of cough variant asthma, 14 cases of upper airway cough syndrome, 10 cases of eosinophilic bronchitis, 9 cases of atopic cough, one case of psychogenic cough, and 37 cases of chronic refractory cough with unknown etiologies; 41 patients were recruited into cough-free GERD group. Their general information was comparable except for cough threshold C2 and C5 which were obviously lower in both GERC and non-GERC groups than in cough-free GERD group (P < 0.05) (Table 1).

4.2. Changes in HRM Variables

Both GERC and cough-free GERD groups presented with a decrease in lower esophageal sphincter pressure, DCI or the proportion of esophageal contraction but a longer break, more frequent large break and higher proportion of failed contraction in GERC and GERD groups when compared with non-GERC group (P< 0.05). However, there were no significant differences in the variables between GERC and cough-free GERD groups (Table 2).

Table 1: General information of study patients.

Characteristics	GERC (n = 51)	Non-GERC (n = 86)	GERD (n = 41)
Gender (male/female)	26/25	44/42	27/14
Age (years)	46.1 ± 15.5	45.8 ± 14.0	49.1 ± 14.4
Disease duration (months)	12.0 (34.5)	24.0 (30.0)	36.0 (54.0)
Cough symptom score			
Daytime	3 (1)	3 (1)	0 (0)*
Night	1 (2)	1 (1)	0 (0)*
C2 (μmol/L)	0.63 ± 0.69	0.70 ± 0.96	3.17 ± 0.21*
C5 (μmol/L)	0.78 ± 1.33	0.96 ± 1.50	35.87 ± 0.31*
FEV1/predicted (%)	97.78 ± 18.07	102.85 ± 14.71	98.4 ± 10.58
FVC/predicted (%)	98.97 ± 14.23	104.26 ± 14.77	97.14 ± 9.25
FEV1/FVC	81.59 ± 9.00	82.93 ± 6.69	85.69 ± 3.82

*P<0.05 compared with GERC and non-GERC groups; C2: the lowest concentration of capsaicin that induces≥2 coughs; C5: the lowest concentration of capsaicin that induces ≥5coughs; GERC: gastroesophageal reflux-induced chronic cough; GERD: gastroesophageal reflux disease; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity.

Table 2: Comparison of HRM variables across the three study groups.

Variables	GERC (n = 51)	Non-GERC (n =86)	Cough-free GERD (n = 41)
UESP (mmHg)	28.30 (20.90, 42.85)	23.20 (13.05, 34.65)	28.40 (21.53, 42.63)
LESP (mmHg)	18.26 ± 12.03*	23.60 ± 13.98	17.31 ± 10.10*
IRP4s (mmHg)	6.76 ± 5.72	7.15 ± 6.18	6.80 ± 4.96
DCI (mmHg.s.cm)	397 (183, 866)*	586 (303, 1226.5)	277 (112.75, 807.25)*
break (cm)	4.10 (1.20, 9.65)*	3.10 (0.55, 6.20)	4.90 (1.10, 10.00)*
DL (s)	6.82 ± 1.02	6.79 ± 1.37	7.13 ± 2.57
Normal contraction (%)	45.0 (0, 90.0)*	60.0 (20.0, 100.0)	40.0 (0, 80.0)*
Weak contraction (%)	20.0 (0, 50.0)	20.0 (0, 50.0)	20.0 (0, 50.0)
Failed contraction (%)	20.0 (0, 50.0)*	0 (0, 30.0)	15.0 (0, 65.0)*
Large break (%)	40.0 (10.0, 72.5)*	10.0 (0, 50.0)	35.0 (0, 90.0)*

*P<0.05 vs non-GERC; DCI: distal contractile integral; DL: distal latency; GERC: gastroesophageal reflux-induced chronic cough; GERD: gastroesophageal reflux disease; IRP4s: 4s integrated relaxation pressure; LESP: lower esophageal sphincter pressure; USEP: upper esophageal sphincter pressure.

4.3. Comparison of MII-Ph Variables

In contrast to non-GERC group, both GERC and cough-free GERD groups showed a significantly higher AET (Figure 1A), SAP (Figure 1B), total reflux episodes (Figure 1C) and the bolus clearance time (Figure 1D) ($P < 0.05$). However, the differences in the variables were not statistically significant between GERC and cough-free GERD groups (Figure 1).

4.4. Comparison Between Acid and Non-Acid GERC

Lower esophageal sphincter pressure was significantly lower in non-acid GERC than that in acid GERC ($P < 0.05$); however, there were no significant differences between the two groups in other HRM variables (Table 3). The patients non-acid GERC more often needed intensive anti-reflux therapy including baclofen to resolve their cough than those with acid GERC ($\chi2 = 4.813$, $P = 0.028$) (Table 3). MII-pH revealed that more total reflux episodes, weakly acidic and weakly alkaline reflux events, but less acid reflux events in non-acid GERC than in acid GERC ($P < 0.05$) (Table 4).

4.5. Comparison Between GERC with Normal And Decreased DCI

When DCI ≥ 450 mmHg.s.cm was used as the cut-off point of normal value, 26 GERC patients with normal DCI and 25 GERC patients with decreased DCI were identified. GERC patients with abnormal DCI showed more severe daytime cough symptoms, lower C5, and higher SAP (Table 5).

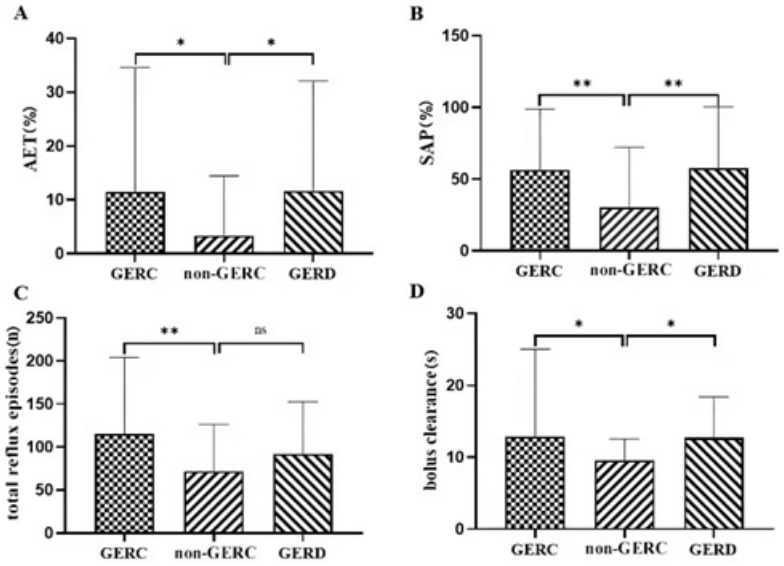

Figure 1: Comparison of acid exposure time (A), symptom association probability (B), total reflux episodes (C), and bolus clearance (D) across the three study groups (*$P < 0.05$; **$P < 0.01$; ns, no statistical significance)

Table 3: Comparison of HRM variables between patients with acid and non-acid GERC.

Variables	Acid GERC (n = 20)	Non-acid GERC (n = 31)
UESP (mmHg)	29.30 (22.65, 47.55)	27.55 (20.70, 38.23)
LESP (mmHg)	23.53 ± 14.12	14.20 ± 10.07*
IRP4s (mmHg)	6.60 (3.60, 13.10)	4.650 (1.58, 8.63)
DCI (mmHg.s.cm)	642 (222, 950)	386 (170, 859)
Peristaltic break (cm)	4.40 (0.80, 9.60)	3.95 (1.58, 9.90)
DL (s)	6.81 ± 1.12	6.82 ± 0.97
Normal contraction (%)	55.0 (12.5, 70.0)	40.0 (0.0, 90.0)
Weak contraction (%)	15.0 (2.5, 50.0)	20.0 (0.0, 52.5)
Failed contraction (%)	20.0 (0.0, 45.0)	20.0 (10.0, 50.0)
Large break (%)	30.0 (0.0, 70.0)	50.0 (10.0, 80.0)
Treatment regimen (standard/intensive)	12/8	9/22*

*P<0.05 vs non-acid GERC group; DCI: distal contractile integral; DL: distal latency; GERC: gastroesophageal reflux-induced chronic cough; RP4s: 4s integrated relaxation pressure; LESP: lower esophageal sphincter pressure; USEP: upper esophageal sphincter pressure.

Table 4: Comparison of MII-pH variables between patients with acid and non-acid GERC.

Variables	Acid GERC (n = 20)	Non-acid GERC (n = 31)
AET (%)	9.30 (0.20, 86.10)	1.00 (0, 3.70) *
SAP (%)	57.6 (0, 85.6)	81.4 (0, 97.0)
Total reflux (n)	66 (16, 126)	1126 (636, 1696) *
Acid reflux (n)	316 (6, 57)	14 (8, 26) *
Weakly acidic reflux (n)	16 (2, 54)	58 (35, 77) *
weakly alkaline reflux (n)	4 (0, 7)	34 (7, 52) *
Gas reflux (n)	14 (4, 30)	36 (25, 58) *
Total proximal reflux (n)	13 (1, 26)	18 (12, 33)
Proximal acid reflux (n)	9 (0, 20)	5 (2, 11)
Proximal weakly acidic reflux (n)	0 (0, 4)	7 (4, 16) *
Proximal weakly alkaline reflux (n)	0 (0,.0)	0 (0, 4) *

*P < 0.05 compared with the non-acid GERC group; AET: esophageal acid exposure time; GERC: gastroesophageal reflux-induced chronic cough; SAP: symptom association probability.

Table 5: Comparison between GERC patients with normal and decreased DCI.

Variables	Normal DCI (n=26)	Decreased DCI (n=25)
Cough symptom score		
Daytime	4 (3, 4)	3 (2, 4) *
Nighttime	1 (1, 2.5)	1 (1, 3)
C2 (μmol/L)	0.71 ± 0.21	0.10 ± 1.00
C5 (μmol/L)	0.49 ± 0.10	0.71 ± 0.21*
AET (%)	2.45 (0.88, 9.15)	1.40 (0.40, 5.20)
Total SAP (%)	91.3 (70.9, 96.9)	0 (0, 93.0) *
SAP for acid reflux (%)	65.0 (0, 89.9)	0 (0, 0) *
SAP for weakly acidic reflyx (%)	46.5 (0, 79.5)	0 (0, 0)
SAP for weakly alkaline reflux (%)	0 (0, 80.0)	0 (0, 0)
DeMeester score	9.20 (3.45, 30.43)	5.41 (1.94, 10.94)
Total reflux episodes (n)	124 ± 96	106 ± 83
Acidic reflux (n)	27 ± 22	25 ± 23
Weakly acidic reflux (n)	57 (116, 83)	41 (13, 76)
Weakly alkaline reflux(n)	7 (5, 39)	13 (1, 48)

*P < 0.05 vs normal DCI; AET: esophageal acid exposure time; C2: the lowest concentration of capsaicin that induces≥2 coughs; C5: the lowest concentration of capsaicin that induces ≥5coughs; DCI: distal contractile integral; GERC: gastroesophageal reflux-induced chronic cough; SAP: symptom association probability.

5. Discussion

The present study has demonstrated that patients with GERC had abnormal lower esophageal sphincter pressure, DCI, proportion of esophageal contractions and failed contractions, break and large break, which were similar to those in patients with cough-free GERD. Therefore, patients with GERC exhibit almost the same esophageal hypomotility as patients with cough-free GERD, which may contribute to the pathogenesis of GERC.

Normal esophageal structure and function are important components of the gastroesophageal reflux defense system [11]. If the pressure of the lower esophageal sphincter is decreased due to its abnormal structure and function, it is easy for gastric contents to backflow into the esophagus and to damage the esophageal mucosa, thereby triggering cough [2]. Several lines of evidence have demonstrated that patients with GERD and GERC often have abnormal lower esophageal sphincter pressure associated with prolonged AET [12-14], which is supported by the findings in the present study. DCI and break in the HRM variables primarily reflect esophageal peristaltic ability and integrity, and a lower DCI is usually accompanied with a significantly higher AET in the patients with GERD [15]. Here, we found that a decreased DCI and proportions of normal peristalsis but increased proportions of failed contractions and large breaks in patients with GERC, concomitant with higher AET and SAP, and a prolonged bolus clearance time; however, no such changes were observed in the cough patients with non-GERC. A decrease in lower esophageal sphincter pressure and impaired esophageal peristalsis are more likely to induce gastroesophageal reflux and aggravate the stimulation of refluxates to the receptors located in esophageal mucosa due to slow clearance and prolonged retention in the esophagus, causing persistent cough via precipitating the esophageal-bronchial

reflex [1, 2]. In the present study, we did not uncover any significant differences in HRM and MII-pH variables between patients with GERC and those with cough-free GERD, indicating that esophageal hypomotility and gastroesophageal reflux severity were similar between the two groups, consistent with the results of our previous study [9], but different from the observations reported by Bennett et al., who found that the frequency of large breaks was significantly higher in GERD patients with cough than that in GERD patients without cough [4]. The discrepancy may be ascribed to the difference of the recruited patients. Bennett et al. selected the GERD patients with cough, who may not have had true GERC, while we enrolled the patients with GERC definitely confirmed by anti-reflux medicinal treatment.

Our findings may help to understand why only a small part of patients with GERD develop into a phenotype of GERC, with a possible underlying mechanism of cough hypersensitivity as indicated by obviously lower cough threshold C2 and C5 to inhaled capsaicin in GERC group than in cough-free GERD group. On the basis of enhanced cough sensitivity, patients with GERC produce an exaggerated cough response to gastroesophageal reflux, which is usually not a tussive stimulus but now becomes a potent cough trigger, leading to development of a specific type of GERD with prominent cough symptom [16]. Airway neurogenic inflammation and mast cell activation may be related to cough hypersensitivity in the patients with GERC [9]. The present study has demonstrated that the lower esophageal sphincter pressure was significantly lower in patients with non-acid GERC than in those with acid GERC. Therefore, to amend abnormal lower esophageal sphincter pressure has become a reasonable strategy for management of non-acid GERC [17]. Our studies have consistently confirmed that baclofen, an inhibitor of transient lower esophageal sphincter relaxations, resolves or relieves cough symptoms in patients with refractory GERC due to non-acid reflux [10, 18-19]. In this study, 71% patients with non-acid GERC required the intensive anti-reflux therapy containing baclofen to achieve their cough improvement, reinforcing the notion that reconstruction of lower esophageal sphincter function is an efficacious option for non-acid GERC. Esophageal dysmotility is not uniform in GERC, as shown by the apparent heterogeneity of DCI. GERC patients with a lower DCI presented with a more severe cough at daytime, an enhanced cough sensitivity and a closer reflux-cough association when compared with GERC patients with normal DCI, suggesting that the level of esophageal hypomotility may have an impact on the manifestation of GERC to some degree. Since the anti-reflux medicinal therapy used in this study included prokinetic agents, it ensures a high success rate for cough resolution but may have also covered the fine differences in intensive anti-reflux therapy implicated by lower DCI [19-20]. There are several limitations in the study. The nature of single-center retrospective study may limit the power of the conclusion. Ideally, the performance of HRM and MII-pH should be repeated after anti-reflux medicinal therapy. Since both procedures are invasive, it is difficult to persuade patients to undergo the examinations again when they have no cough symptom. Thus, the possible recovery of abnormal esophageal function in response to effective treatment needs a further confirmation in the patients with GERC. In conclusion, patients with GERC have an impaired esophageal motility as measure by HRM, which may contribute to the mechanisms underlying cough and response to anti-reflux therapy. To rectify the esophageal dysfunction may greatly improve the outcome of anti-reflux therapy in the patients with GERC.

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