High resolution esophageal manometry and life exposure factors in non-cardiac chest pain patients with refractory gastroesophageal reflux disease

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Abstract

Background: Refractory gastroesophageal reflux disease (RGERD) is defined by the presence of troublesome GERD symptoms despite proton pump inhibitors (PPIs) treatments for 8-12 weeks. Non-cardiac chest pain (NCCP) is the most common atypical presentations. This study was aimed at clarifying the features of High Resolution Esophageal Manometry (HREM) and life exposure factors of NCCP in RGERD patients for guiding further therapeutic strategies. **Methods:** 83 RGERD patients were enrolled, in which 44 patients afflicted with NCCP as P group and 39 patients without NCCP as NP group. According to the endoscopy results, P group was further divided into reflux esophagitis group (RE group), non-erosive reflux disease group (NERD group) and Barrett's esophagus group (BE group). HREM was performed to assess esophageal motility. Diverse questionnaires were conducted to evaluate severity of symptoms, quality of life, risk factors, degrees of anxiety and depression and so on. **Results:** a) Average resting pressures of the lower esophageal sphincter (LES), residual pressures of the LES and the esophageal distal contractile integral (DCI) score in P group were significantly lower than those in NP group ($p < 0.05$). b) Average resting pressures of the upper esophageal sphincter (UES), residual pressures of the UES, lengths of the LES and the UES showed no difference between the two groups ($p > 0.05$). c) Compared with NP group, the patients in P group had higher exposure to alcohol, coffee, sweets, overeating and stress ($p < 0.05$). d) Anxiety and depression status of patients in P group were remarkably severer than those in NP group ($p < 0.05$). e) The pain intensity in RE group and BE group was higher than NERD group ($P < 0.05$), while there was no difference between RE group and BE group ($P > 0.05$). **Conclusions:** Esophageal motility related anti-reflux barriers are much weaker in the RGERD patients with NCCP than those without NCCP, which mainly presents as the much lower average resting and residual pressures of the LES and DCI. Alcohol, coffee, sweets, overeating, stress, anxiety and depression are risk factors of RGERD-related NCCP. It's suggested that the recovery of anti-reflux barriers and the avoidance of risk factors may be essential therapeutic strategies for improving the curative effect.

Background

Gastroesophageal reflux disease (GERD) refers to one of the common clinical digestive diseases caused by stomach and duodenal contents flowing back into the esophagus and characterized by heartburn and acid reflux [1]. Because of the improvements of living standards and the changes of lifestyles, GERD is prevalent worldwide with its incidence increasing year by year [2]. Although the uncomfortable symptoms of GERD patients can be mostly relieved by conventional proton pump inhibitors (PPIs), there are still 10% - 40% GERD patients whose symptoms such as reflux, chest pain etc. cannot be obviously relieved after double dose of PPI treatment for 8–12 weeks, which is named refractory gastroesophageal reflux disease (RGERD) [3,4]. When those troublesome symptoms can't be improved with GERD therapy, High Resolution Esophageal Manometry (HREM) are often performed to assess peristalsis and to detect alternative major motor disorders in the setting of GERD.

GERD is associated with a broad spectrum of symptoms, which can be split into the typical symptoms such as heartburn and acid regurgitation and the atypical symptoms such as non-cardiac chest pain

(NCCP), chronic cough, hoarseness, and asthma [5]. It's reported that presence of GERD was strongly associated with NCCP in the community [6]. The average annual prevalence of NCCP in the general population is approximately 25%, making NCCP the most common atypical presentation of GERD [7]. At present, the reports on RGERD are not adequate, what's more, they mainly display the differences of overall symptoms between RGERD and non-RGERD patients, whereas the investigation of a certain symptom of RGERD has been rarely reported. With the objective of further clarifying the characteristics of esophageal motility according to the Chicago Classification (CC) v3.0 [8] and risk factors of NCCP in RGERD patients, the study retrospectively analyzed 83 RGERD patients in order to guide further therapeutic modalities.

Methods

Study subjects

This study analyzed 83 patients with RGERD who were performed using HREM in Gastrointestinal Motility Suit, in First Affiliated Hospital of Dalian Medical University from February 15, 2016 to January 22, 2017. On the basis of whether with NCCP, they were divided into chest pain group (P group) and non-chest pain group (NP group). The P group was further divided into reflux esophagitis group (RE group), non-erosive reflux disease group (NERD group) and Barrett's esophagus group (BE group) according to the results of endoscopy.

Inclusion and exclusion criteria

Inclusion criteria a. The diagnostic criteria of RGERD follows the consensus of Chinese gastroesophageal reflux disease experts [4] and NCCP is defined as recurrent angina-like or substernal chest pain believed to be unrelated to the heart. b. the gastroscopy and HREM examination and/or 24-hour PH-metry had been completed; c. the discomfortable symptoms had been relieved after alternative PPIs and/or combining prokinetic drugs (Itopride Hydrochloride/topride) treatments, which were guided according to the results of HREM. Meanwhile, patients had no history of antianxiety and antidepressant drugs during these period.

Exclusion criteria a. Accompanied by malignant tumor, immune system disease, metabolic disease, heart and lung diseases and severe local infection, etc.; b. endoscopic findings of esophageal ulcer, or esophageal hiatus hernia; c. accompanied by high pressure esophagus such as diffuse esophageal fistula and achalasia; d. performed gastroesophageal surgery or abdominal surgery before; e. accompanied by mental illness, communication disorder, or unconsciousness. f. diagnosed other esophageal dynamic disorders by HREM, such as hiatal hernia. g. failed to finish all the related tests and questionnaires.

Questionnaires

The questionnaires were conducted under the guidance of the same doctor who was present to confirm that the participants understood the forms clearly. However, the doctor was prohibited from using any suggestive words regardless of any questions.

General information

The general datas included patient's name, gender, age, height, weight, past disease history, history of medication, history of diagnosis and treatment, etc. Body mass index [BMI] was calculated by dividing the weight (in kg) by the height (in meters) squared.

Extra-esophageal manifestations questionnaire [5]

The GERD related extra-esophageal symptoms questionnaire was used to record the incidence of chronic cough, hoarseness, pharyngeal discomfort and asthma.

The reflux diagnostic questionnaire (RDQ) [9]

Statistics on the incidence of heartburn, acid reflux, antifeeding, chest pain, etc. in the past 4 weeks. Frequency score: asymptomatic 0 point, symptom frequency <1d / week, 1d / week, 2 ~ 3d / week, 4 ~ 5d / week and 6 ~ 7d / week were counted as 1, 2, 3, 4, 5 points. Symptom score: no, very light, slightly light, moderate, slightly heavy, severe represented by 0, 1, 2, 3, 4, 5 points. Symptom score standard: 1 point: not obvious, found under the doctor's reminder; 3 points: obvious, daily activities were disturbed, even needed medication; 5 points: very serious, couldn't complete daily activities, must be treated with long-term medication; 2 points: symptoms between 1 and 3; 4 Points: symptoms between 3 and 5. Calculating the total score.

Short-form McGill pain questionnaire (SF-MPQ) [10]

0 point: no pain; 1 point: slight pain; 2 points: discomfort pain; 3 points: oppression pain; 4 points: severe pain; 5 points: extreme pain.

SF-36 quality of life scale [11]

The questionnaire contains 36 items and eight dimensions, including physical functioning (PF), role-physical (RP), bodily pain (BP), general pain (GH), vitality (VT), social functioning (SF), role-emotional (RE), and mental health (MH). The former four dimensions were called physical health components (PHC), and the latter four dimensions were called mental health components (MHC). Scoring method: final score = (actual score - lowest score) / (highest score - lowest score) × 100.

Life exposure factors questionnaire [12–14]

In order to learn about the habits of diet and lifestyle, a self-designed life exposure factors questionnaire were conducted, including smoking, drinking, strong tea, coffee, sweets, greasy food, overeating, spicy food, high salt, staying up late, fatigue and stress.

Zung self-rating anxiety scale (SAS) [15] and Zung self-rating depression scale (SDS) [16]

Subjects selected options based on actual conditions in the past weeks. The frequency of occurrence of different symptoms was assessed by four grades of scoring criteria. A: no or very little time; B: sometimes; C: most of the time; D: most or all of the time. The positive expressions in the scale were scored in the order of 4 to 1, and the negative expression in the scale were scored in the order of 1 to 4. Applying the conversion formula to convert the total score from each entry into the final score. The total score of each item was multiplied by 1.25, and the integer part was the final score. The SAS final score ≥ 50 points was considered to have an anxiety state, and the SDS final score ≥ 53 points was considered to have a depression state.

Esophageal motility measurement

HREM studies were performed according to the standardized protocol as used previous studies in our center, using a 24-channel water-perfused catheter of 4.0 mm in diameter [17] (Ningbo Maida Medical Device Inc., Ningbo, China). The specific operational method is the same as the previous experiment [17]. The resting pressure, residual pressure and lengths of the upper esophageal sphincter (UES) and the low esophageal sphincter (LES), as well as the esophageal distal contractile integral (DCI) were recorded.

Statistical analysis

All data was input into SPSS 19.0 software package for processing. The count data was converted into a percentage and analyzed by the chi-square test. The measurement data were expressed as mean $\pm$ standard deviation ($\bar{x} \pm s$) and analyzed by t test. The significance level for all hypothesis testing (p-value) was 0.05.

Results

General data of subjects

A total of 83 patients with RGERD were enrolled in the study, including 44 patients in the chest pain group (P group), accounting for 53%, and 39 patients in the non-chest pain group (NP group), accounting for

47%. The gender comparison ($\chi^2 = 0.507$, $p = 0.476$), age comparison ($t = 1.098$, $p = 0.275$) and BMI comparison ($t = -0.547$, $p = 0.586$) were not statistically significant ($p > 0.05$, Table 1).

Comparison of extra-esophageal manifestations between P group and NP group

The incidences of chronic cough, hoarseness and pharyngeal discomfort in P group were higher than those in NP group ($p < 0.05$). No statistical difference was noted in the incidence of asthma between the two groups ($p > 0.05$). (see Table 2).

Comparison of RDQ scores between P group and NP group

The RDQ scores of P group 22.55 ± 3.454 were higher than those of NP group 17.64 ± 3.048 . The difference was statistically significant ($p < 0.05$, Fig. 1a).

Comparison of pain intensity between different types of endoscopy in P group

In P group, 10 patients were in RE group, accounting for 22.7%, 29 patients in NERD group, accounting for 65.9%, 5 patients in BE group, accounting for 11.4%. The pain intensity among the three groups were compared (see Fig. 1b). The pain intensity in RE group and BE group were higher than NERD group ($P < 0.05$), however, between RE group and BE group, there was no difference ($P > 0.05$).

Comparison of quality of life

Between P group and NP group, there were significant differences in both physical health and mental health, which totally included eight dimensions ($p < 0.05$, Fig. 1c).

Analysis of life exposure factors

The exposure incidences of smoking, drinking, strong tea, coffee, overeating, sweets, greasy food, spicy food, high salt and stress in P group were higher than those of NP group. Among them, drinking, coffee, overeating, sweets, and stress between the two groups were significantly different ($p < 0.05$), nevertheless, the remaining items were not statistically different. (see Table 3).

Analysis of anxiety and depression state

The incidences of anxiety and depression in P group were significantly higher than those in NP group ($p < 0.05$, Table 3).

Comparison of esophageal manometry results between P group and NP group

Images of esophageal pressure measurements

Typical images of esophageal motility measurements in P group and NP group were presented (see Fig. 2a, 2b).

Analysis of esophageal manometry data

The average resting and residual pressures of the LES and the esophageal DCI in P group were lower than those in NP group ($p < 0.05$, Fig2f, 2g and 2i). The average resting and residual pressures of the UES and the lengths of the LES and the UES showed no difference between P group and NP group ($P > 0.05$, Fig. 2c–2e, and 2h).

Discussion

GERD is the most common underlying mechanism of NCCP, with an estimated prevalence ranging from 30% to 60% [18–20]. In fact, RGERD-related NCCP also takes a large percentage. The study shows that a) Average resting pressures of the LES, residual pressures of the LES, and the DCI in P group were significantly lower than those in NP group ($p < 0.05$). b) Average resting pressures of the UES, residual pressures of the UES, lengths of the LES and the UES showed no difference between P group and NP group ($p > 0.05$). c) Compared with NP group, the patients in P group had higher exposure to alcohol, coffee, sweets, overeating and stress ($p < 0.05$). d) Anxiety and depression status of patients in P group were remarkably severer than those in NP group ($p < 0.05$). e) The pain intensity in RE group and BE group was higher than NERD group ($P < 0.05$), while there was no difference between RE group and BE group ($P > 0.05$).

The results of esophageal manometry, reflux symptom index, mental state, extra-esophageal manifestations, questionnaires such as life exposure factors and life quality were summarized to provide a more detailed understanding of RGERD-related NCCP and a further reference for clinical therapy.

Etiological factors of GERD contain dysfunction of the esophagogastric junction (EGJ), which comprises ineffective acid and bolus clearance, increased intragastric pressure, and anatomical changes of the EGJ, such as a hiatal hernia, resulting in mucosal injury [21,22]. Insufficient inhibition of gastric acid secretion, ongoing weakly acidic or non-acid reflux and reflux sensitivity are the major causes of RGERD symptoms[3]. In addition, transient lower esophageal sphincter relaxations (TLESRs) are considered as a

main mechanism behind acidic, weakly acidic, and weakly alkaline reflux episodes in both healthy populations and patients with GERD [23,24]. HREM is usually completed in order to evaluate the structure and function of the EGJ, given its anti-reflux barrier property. The EGJ is a complex structure composed of the crural diaphragm and the LES [25]. As is shown in the study, the resting pressure and the residual pressure of the LES in P group were lower than those in NP group ($P < 0.05$). Because of the low pressure of the LES, reflux is prone to happen. Thereby, it is speculated that reflux may play important roles in the occurrence of NCCP. The DCI itself represents the strength of the smooth muscle contraction wave at the distal end of the esophagus. When the peristaltic force is reduced, the ability to clear the bolus is worse [26]. In this study, the DCI of P group (2158.8 ± 1154.3) was lower than that of NP group (3057.5 ± 1729.9) ($P < 0.05$). Although both were in the normal range, the difference was statistically significant. Consequently, we speculated that the NCCP in RGERD patients may be related to ineffective acid and bolus clearance, owing to the decrease of DCI. Because CC v3.0 doesn't contain the TLESRs, we didn't take it into account at that time, which should be studied in the future research.

The RDQ scale is a retrospective statistic for the problems related to reflux symptoms to help diagnose GERD, with a high sensitivity and specificity [27]. It's generally assumed that the higher the score of RDQ is, the more serious the reflux is. Compared with NP group, the RDQ score of P group was relatively higher ($P < 0.05$), indicating that the reflux might be the cause of NCCP. Because not all patients had performed the 24-hour PH-metry, for example, those patients with severe esophagitis (LA-C and LA-D) don't need to perform it to diagnose reflux. so we didn't analyse the data of 24-hour PH-metry owing to the limited data.

According to endoscopic results, GERD can be divided into RE, NERD and BE [3]. In the 44 patients with RGERD-related NCCP, the number of the RE group, the NERD group and the BE group accounted for 22.7%, 65.9%, 11.4%, respectively, which is accordance with the outcome of previous studies that NERD takes the largest proportion in GERD [28]. Studies have demonstrated that severity and/or frequency of GERD symptoms cannot predict the presence or absence of esophageal mucosal injury [29]. Nevertheless, the pain intensity of the RE group and the BE group were higher than the NERD group ($P < 0.05$). And there was no significant difference in pain intensity between the RE group and the BE group ($P > 0.05$). It's widely accepted that frequent and strong esophageal acid perfusion may trend to cause the occurrence of RE and BE, thereby it's speculated that the intensity of NCCP is closely related to the frequency and severity of acid reflux. The mechanisms of NCCP in RGERD patients are poorly understood. It has been suggested that the pain hypersensitivity within esophagus may be a factor in the generation of NCCP [30]. It has been reported that after the lower esophagus was acid-infused, the pain threshold of the upper esophagus and chest wall could be reduced [31]. Long-term reflux and repeated recurrence of inflammation may lead to destruction of the mucosal barrier, as well as the decline of pain threshold, making the symptoms of NCCP more serious.

It's reported that patients with GERD have a high probability of experiencing extra-esophageal manifestations [5]. In this study, the incidences of chronic cough, hoarseness and pharyngeal discomfort in P group were higher than those in NP group ($P < 0.05$). It appears that RGERD patients with NCCP are more possible to be accompanied by discomforts of chronic cough, hoarseness and pharyngeal

discomfort, which indicates that these extra-esophageal manifestations may have the common pathogenesis.

Health consists of not only physiological health, but also mental health and social well-being. In this study, Chinese Version SF-36 Life Quality Scale was used to assess the impact of NCCP on patients' quality of life (QOL). The results showed that P group was in worse stage than NP group in both physical health and mental health ($P < 0.05$). There were statistical differences in each dimension, suggesting that NCCP had negative effects on patients. Shelby et al [32] pointed out that for NCCP patients, chest pain, anxiety and fear of pain formed a vicious circle, resulting in physical and social psychological disorders, thereby reducing the QOL. Accordingly, improving the control of RGERD symptoms can improve QOL of patients.

Psychological state is closely related to the occurrence of GERD. Some investigations showed that anxiety and depression could cause the occurrence of GERD, especially NERD [33], and some studies showed that NERD patients often had poor effects on acid suppression owing to mental stress, anxiety and depression [34]. In this study, we found that the anxiety and depression states of P group were significantly worse than those of NP group, showing that there is a link between anxiety and depression states and RGERD-related NCCP. Psychological factors are crucial for the occurrence and progression of RGERD. On the contrary, NCCP lead to or aggravate RGERD patients' symptoms, anxiety or depression, or both.

It's widely believed that lifestyle and dietary habits affect the occurrence of GERD. Studies [35] have shown that smoking and drinking could result in LES pressure decline and triggering or aggravating GERD symptoms. In order to clarify the differences in lifestyle and dietary habits in RGERD patients with and without NCCP, 12 life exposure factors were counted in the study. The result showed that the incidences of life exposure factors such as smoking, drinking, strong tea, coffee, overeating, sweets, greasy food, spicy food, high salt and stress in P group were higher than those in NP group ($P < 0.05$). It can be speculated that life exposure factors affect the occurrence of NCCP in RGERD patients. lifestyle and dietary habits changes are warranted to avoid these exposure factors if present.

In general, it's suggested that the recovery of anti-reflux barriers, the avoidance of exposure factors, the improvement of psychological state as well as the changes of lifestyle and dietary habits may be essential therapeutic strategies for increasing the curative effect in patients with RGERD-related NCCP. However, any of these aforementioned modifications alone is unlikely to eliminate all symptoms. Luckily, with the development of medical and invasive therapy, that will further expand GERD therapy [36]. It's thus essential to combine multiple therapy treatments together for the patients with RGERD-related NCCP.

The deficiencies of the study are: a) The number of recruited patients was limited, so a multi-center and larger sample study will be necessary. b) This study lacked the healthy control group because the invasive examination (HREM) was difficult to be accepted.

Conclusions

Esophageal motility related anti-reflux barriers are much weaker in the RGERD patients with NCCP than those RGERD patients without NCCP, which mainly presents as the much lower average resting and residual pressures of the LES and DCI. Alcohol, coffee, sweets, overeating, stress, anxiety and depression are risk factors of RGERD-related NCCP. It's suggested that the recovery of anti-reflux barriers and the avoidance of risk factors may be essential therapeutic strategies for improving the curative effect.

List Of Abbreviations

RGERD: Refractory gastroesophageal reflux disease; GERD: Gastroesophageal reflux disease; NERD: Non-erosive reflux disease; PPIs: Proton pump inhibitors; NCCP: Non-cardiac chest pain; CC: Chicago Classification; HREM: High Resolution Esophageal Manometry; LES: Lower esophageal sphincter; UES: Upper esophageal sphincter; DCI: Distal contractile integral; RE: Reflux esophagitis; NERD: Non-erosive reflux disease; BE: Barrett's esophagus; RDQ: Reflux diagnostic questionnaire; SF-MPQ: Short-form McGill pain questionnaire; PF: physical functioning; RP: role-physical; BP: bodily pain; GH: general pain; VT: vitality; SF: social functioning; RE: role-emotional; MH: mental health; PHC: physical health component; MHC: mental health components; EGJ: Esophagogastric junction; TLESRs: Transient lower esophageal sphincter relaxations; QOL: Quality of life.

Declarations

Ethics approval and consent to participate: The Ethics Committee of First Affiliated Hospital of Dalian Medical University Ethical approved the report of scientific research project. It confirmed that project program and informed consent were reviewed. All the human subjects in the study had signed the informed consent. (Approval number: KSKY2018–67).

Consent for publication: Not applicable.

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Authors' contributions: Study concept and design: YL, ZD, LW. Acquisition of data, analysis and interpretation of data: YL, PL, ZZ, LW, XS, DY, LW. Drafting of the manuscript: YL, PL, ZZ, LW, XS, DY, LW, ZD. Critical revision of the manuscript for important intellectual content: YL, PL, ZD. Statistical analysis: YL. Administrative, technical, or material support: YL, PL, ZZ, LW, XS, DY, LW, ZD. Study supervision: ZD. Final approval of the version to be published: YL, PL, ZZ, LW, XS, DY, LW, ZD.

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Tables

Table 1. The general data of subjects

Group	N	Gender♂M/F	Age♂years	BMI♂Kg/m2
P group	44	18/26	51.45±13.90	23.67±3.56
NP group	39	13/26	54.67±12.60	23.23±3.70

Table 2. Comparison of extra-esophageal symptoms

Extra-esophageal symptoms	P group N=44	NP group N=39	χ^2	<i>p</i>
Chronic cough	25[56.8%]	13[33.3%]	4.594	0.032
Hoarseness	15[34.1%]	5[12.8%]	5.114	0.024
Pharyngeal discomfort	33[75.0%]	19[48.7%]	6.103	0.013
Asthma	3[6.8%]	1[2.6%]	0.816	0.366

Table 3. Comparisons of life exposure factors, anxiety and depression between P group and NP group

Exposure factors	P group n=44	NP group n=39	χ^2	<i>p</i>
Smoking	16[36.4%]	12[30.8%]	0.289	0.591
Drinking	32[72.7%]	18[46.2%]	6.095	0.014
Strong tea	10[22.7%]	7[17.9%]	0.290	0.590
Coffee	20[45.5%]	8[20.5%]	5.753	0.016
Overeating	31[70.5%]	19[48.7%]	4.078	0.043
Sweets	33[75.0%]	19[48.7%]	6.103	0.013
Greasy food	24[54.5%]	15[38.5%]	2.147	0.143
Spicy food	27[61.4%]	19[48.7%]	1.338	0.247
High salt	24[54.5%]	17[43.6%]	0.993	0.319
Staying up late	12[27.3%]	11[28.2%]	0.009	0.925
Fatigue	14[31.2%]	14[35.9%]	0.154	0.695
Stress	30[68.2%]	16[41.0%]	6.171	0.013
SAS ≥50	30[68.2%]	18[46.2%]	4.114	0.043
SDS ≥53	27[61.4%]	15[38.5%]	4.338	0.037

Figures

Figure 1

RDQ scores, the intensity of chest pain and quality of life in patients with RGERD. a Comparison of RDQ scores between P group and NP group; b Pain intensity in 3 subgroups of P group; c Comparison of quality of life between P group and NP group.

Figure 2

Typical high resolution esophageal manometric measurements and esophageal manometric parameters between two groups. a The typical image of HREM in P group; b The typical image of HREM in NP group c Average resting pressure of the UES in two groups; d Average residual pressure of the UES in two groups; e The lengths of the UES in two groups; f Average resting pressure of the LES in two groups; g

Average residual pressure of the LES in two groups; h The lengths of the LES in two groups; i The DCI in patients in two groups.