Impaired Esophageal Mucosal Integrity and the Related Motility Factors in Refractory Gastroesophageal Reflux Disease

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Abstract

Backgrounds. Research on esophageal mucosal integrity in gastro-oesophageal reflux disease (GERD) has been taken seriously in recent years, especially in refractory GERD. Mean nocturnal baseline impedance (MNBI) is proposed as an indicator of impaired mucosal integrity. We aimed to compare the MNBI value and investigate the impact of esophageal motility on MNBI in different subtypes of refractory GERD.

Methods. Endoscopy, high-resolution manometry, and 24h impedance-pH monitoring were performed in 412 refractory GERD patients. From these patients, 94 erosive esophagitis (EE), 52 non-erosive reflux disease (NERD), and 31 Barrett's esophagus (BE) patients were enrolled in the study. EE group 54 included Los Angeles (LA) Grade-A/B and 40 LA Grade-C/D patients. 52 functional heartburn (FH) patients were used as the control. MNBI was acquired at 3 and 5 cm above lower esophageal sphincter (LES) and was compared between groups. Parameters of esophagogastric junction (EGJ) and LES, along with esophageal peristaltic sequences were recorded. Univariate and multivariate regression analysis were performed to determine the impact of these motility factors on MNBI in different subtypes of refractory GERD.

Results. MNBI values were significantly lower in all subgroups of refractory GERD patients than in FH patients. MNBI in NERD patients was similar with LA-A/B and LA-C/D patients. MNBI in NERD and LA-C/D patients was significantly lower than in BE patients. No difference in MNBI was found between LA-A/B and BE patients. Ineffective esophageal motility and absent contractility were the risk factor for decreased MNBI in LA-A/B and LA-C/D patients, respectively. Type III EGJ (hiatus hernias) and decreased LES length were the risk factor for decreased MNBI in NERD and BE patients, respectively.

Conclusions. Impaired mucosal integrity of NERD patients was as severe as that of EE patients and hiatus hernias were the risk factor, therefore, mucosal protections and explorations of hiatus hernias should be emphasized in refractory NERD patients. Weakened esophageal body peristalsis and decreased LES length were the risk factor for the impaired mucosal integrity of refractory EE patients and BE patients, respectively, and thus the therapy on peristaltic disorders and LES function was recommended for them. These results provided new ideas for optimizing the treatment of refractory GERD.

Background

Gastro-oesophageal reflux (GERD) is a series of symptoms and complications caused by stomach and duodenal contents flowing back into the esophagus, and there are three types of GERD, including erosive esophagitis (EE), non-erosive reflux disease (NERD), and Barrett's esophagus (BE) [1, 2]. About 9%-57.6% of adult experience reflux symptoms every year in the world [3]. The diagnostic methods of GERD conclude clinical history and questionnaires, proton pump inhibitors (PPIs) trials, endoscopy and ambulatory reflux monitoring. PPIs are proposed as the first-line therapy for GERD in clinic and have

shown clinical efficacy in approximately 80% of EE patients [4]. Nevertheless, about half of NERD patients with daily PPIs treatments still complain of symptoms [5, 6]. The symptoms, such as heartburn and regurgitation, which are not relieved after 8–12 weeks of double dose PPIs treatments, are called refractory GERD [7, 8]. Reflux hypersensitivity, non-acid reflux, reflux clearance obstacles, and many other factors result in PPI failure, among which impaired mucosal integrity plays a significant role [9]. Poor response of PPI and persistent symptoms were found to be associated with esophageal mucosal impairments and ultrastructural alteration in patients with refractory GERD [10–12].

The morphological and functional impairments of esophageal mucosal integrity, such as dilated intercellular space (DIS), basal cell hyperplasia, tight junction protein changes, and increased epithelial permeability in GERD patients, have been widely recognized. However, the detection of such alterations is difficult to be applied in clinic [13, 14]. Multichannel intraluminal impedance-pH (MII-pH) monitoring is usually used to detect reflux episodes of GERD patients. When there is no reflux or swallowing attack, the esophageal wall will contact the MII-pH sensor catheter directly, and the impedance at this time reflects the inherent conductivity of esophageal wall, that is, the baseline impedance (BI). The decreased value of BI reflects the impairment of mucosal integrity caused by reflux [15, 16]. Considering that frequent reflux and swallowing activities disturb the measurement during daytime, mean nocturnal baseline impedance (MNBI), the average BI value of three 10 minutes' measurement at night (around 1:00, 2:00, and 3:00 AM) was then applied [17]. This retrospective study intended to investigate the characteristic of impaired esophageal mucosal integrity represented by decreased MNBI and the respective motility factors in refractory EE, NERD and BE patients based on high-resolution esophageal manometry (HREM) and MII-pH monitoring, in order to provide ideas for optimizing the treatment of refractory GERD.

Methods

Patient Selection

412 adult patients (18–80 years) with reflux symptoms who failed double dose of PPIs for 8–12 weeks received upper gastrointestinal endoscopy (CV-260/290, Olympus, Japan), HREM (GAP24A, Maida, China) and 24h MII-pH (JSIps-1, Jinshan, China) monitoring off-PPI at the Department of Endoscopy and Gastrointestinal Motility Center in the First Affiliated Hospital of Dalian Medical University during January 1, 2019, to October 31, 2020. Patients with incomplete data, reflux hypersensitivity, eosinophilic esophagitis, connective tissue disease, prior foregut surgery, history of carcinoma, obstruction of outflow tract, Jackhammer esophagus, and distal esophageal spasm were excluded. Finally, 177 patients diagnosed with refractory GERD were enrolled in this study, including 94 EE, 52 NERD, and 31 BE patients. 94 EE patients were grouped into Los Angeles Grade A or B (LA-A/B, n = 54) and Grade C or D (LA-C/D, n = 40). 52 functional heartburn (FH) patients who were matched for age, sex, height, and body mass index (BMI) with refractory GERD patients and had no motility disorders were selected for the control group. The study was approved by the ethical committee of The First Affiliated Hospital of Dalian Medical University (Serial No. PJ-KS-KY-2018-94(x)).

Diagnostic Criteria

Patients with endoscopic mucosal breaks were diagnosed with EE. Patients with normal endoscopy and abnormal acid exposure were diagnosed with NERD. BE patients were confirmed by the columnar metaplasia of distal esophagus, whether intestinal type or not [18]. FH patients were confirmed by normal endoscopic manifestations, normal acid exposure, and negative symptom association [19]. It was reported that there was no difference in BI values, intercellular spaces and microscopic histological lesions between FH patients and healthy people [17, 20, 21]. FH patients were therefore used as the control group, and the decreased MNBI in refractory GERD patients compared with FH patients ($p < 0.05$) was supposed to represent the impaired mucosal integrity in this study.

Endoscopic Examination

According to the Los Angeles classification, EE was divided into four grades based on the degree of esophageal mucosal breaks through an endoscopy review [22]. Grade A: 1 or more mucosal breaks confined to the mucosal folds and no longer than 5 mm in length. Grade B: 1 or more mucosal breaks more than 5 mm in length, but not continuous between the two mucosal folds. Grade C: continuous mucosal breaks no more than 75% of the esophageal circumference. Grade D: continuous mucosal breaks more than 75% of the esophageal circumference.

BE was diagnosed by endoscopy with pathological biopsies. The salmon color columnar epithelium, which displaced the pink squamous epithelium ≥ 1 cm above esophagogastric junction (EGJ) was distinguished under endoscopy, then 2 biopsy samples were taken below the squamous-columnar junction from each patient. Most patients were short-segment BE and showed tongue like projection instead of circumferential manifestation in our study, therefore biopsies were not carried out as the Seattle protocol of four-quadrant biopsy [23, 24].

HREM Measurement

HREM with a 24-channel water-perfused catheter of 4.0 mm in diameter was utilized as previously described [25]. Patients were asked to fast foods for 12 h and water for 6 hours before the examination. Drugs interfering esophageal motility were suspended temporarily. Patients were asked to stay in a supine position and underwent 10 swallows of 5 ml water with a 30 seconds interval under ambient temperature [17]. Esophageal motility parameters were analyzed by the computer software (MedView360 V2.1) combined with Chicago Classification version (CCv) 4.0 [26].

Contraction vigor of esophageal body was evaluated by distal contractile integral (DCI). Swallows were defined as normal ($DCI > 450$ mmHg•cm•s and < 8000 mmHg•cm•s), weak ($DCI > 100$ mmHg•cm•s and < 450 mmHg•cm•s), or failed ($DCI < 100$ mmHg•cm•s), and a swallow with a large break (length > 5 cm) in the 20mmHg isobaric contour and $DCI > 450$ mmHg•cm•s was defined as fragmented. Weak, failed and fragmented swallows were all defined as ineffective. The diagnosis of ineffective esophageal motility (IEM) is defined as $\geq 70\%$ ineffective swallows or $\geq 50\%$ failed swallows. Absent contractility was defined as normal median integrated relaxation pressure (IRP) and 100% failed swallows. The morphology of EGJ depends on the relationship between lower esophageal sphincter (LES) and crural

diaphragm (CD). Type I EGJ had overlapped LES and CD without separation, type II EGJ had a 1–2 cm separation between LES and CD, and type III EGJ had a > 2 cm separation between LES and CD. Type III EGJ was consistent with radiographically evident hiatus hernia. The vigor of EGJ barrier was measured over 3 consecutive respiratory cycles above the gastric pressure with a method analogous to that for evaluating DCI. It was then divided by the duration of 3 respiratory cycles to yield the EGJ contractile integral (EGJ-CI) independent of time. EGJ-CI of less than 25 mmHg•cm was considered hypotensive [26]. IEM, absent contractility, EGJ morphology, EGJ-CI, LES length, LES resting pressure, and IRP were recorded.

MII-pH Monitoring

II-pH monitoring was performed off acid inhibitor for at least 7 days. HREM was used to locate LES. pH sensors of MII-pH catheter were positioned 5 cm above the LES, and impedance electrodes were positioned at 3, 5, 7, 9, 15, and 17 cm above the LES. Distal MNBI was measured at both 5 cm and 3cm above LES [27, 28, 29]. Esophageal reflux parameters were analyzed by the computer software (JSG.Zp.PlatformUI, Jinshan, China).

Acid exposure was defined as abnormal if acid exposure time (AET) was beyond 6% and normal if AET was under 4%. When AET was between 4% and 6%, reflux events were used as an adjunctive metric, which was abnormal when > 80 per 24h and normal when < 40 per 24h [2]. Symptom association was determined as positive when symptom association probability (SAP) $\geq$ 95% or symptom Index (SI) $\geq$ 50%, otherwise negative [19]. AET, reflux events, SAP, and SI were recorded.

Statistical Analysis

Categorical variables are presented as frequencies and proportions, while continuous variables are expressed as mean $\pm$ standard error (normal distribution) or as median with interquartile ranges (non-normal distribution). Chi-square tests were used for categorical variables. Kruskal-Wallis tests were used for continuous variables. Between-group comparison was performed using T test or Mann-Whitney U test. Univariate and multivariate liner regression analysis was performed to identify motility related risk factors for impaired mucosal integrity, in which MNBI was taken as outcome variables and motility parameters were taken as dependent variables. Differences were confirmed as statistically significant when $P < 0.05$. The statistical analysis was performed with SPSS software (version 20.0; IBM Corp, Armonk, NY, USA).

Results

Clinical Characteristics of Patients

There was no statistical difference in age, sex, height, and BMI in the 5 groups (all $P > 0.05$). The proportion of IEM, absent contractility, type III EGJ, and hypotensive EGJ-CI (Figure.1) was higher in refractory GERD patients than in FH patients (all $P < 0.05$). Differences in LES resting pressure and IRP were also found in the 5 groups (both $P < 0.05$) (Table.1).

Comparison of MNBI between Groups.

The median value of MNBI at 5cm of the LA-C/D, LA-A/B, NERD, BE and FH patients were as follows: 1026.5 (729.0-1685.0), 1690.5(1124.3-2347.5), 1155.5(972.3-2027.5), 2163.0(1223.0-2984.0), 2714.0(1989.5–3262.0)Ω, respectively (Figure.2-a). The median value of MNBI at 3cm of the LA-C/D, LA-A/B, NERD, BE and FH patients were as follows: 955.0(707.8-1628.8), 1410.0(884.5–2140.0), 1003.0(746.3-1726.3), 1960(981.0-2834.0), 2606.0(1985.5–3421.0) Ω, respectively (Figure.2-b). Compared to FH patients, all four groups of GERD patients had significantly decreased MNBI values at both 5 and 3 cm above LES (all $P < 0.05$). MNBI values in LA-C/D patients were lower than in LA-A/B patients at 5 cm above LES and lower than in BE patients at both 5 and 3 cm above LES (all $P < 0.05$). MNBI values in NERD patients were lower than in BE patients at 3 cm above LES ($P < 0.05$) and there was a trend at 5cm above LES ($P = 0.053$). No difference in MNBI values was found between LA-A/B and BE, between LA-A/B and NERD, or between LA-C/D and NERD (all $P > 0.05$).

Linear Regression Analysis of MNBI in GERD

A significant decrease in MNBI values was found in all refractory GERD patients, then stepwise linear regression models were created to distinguish the motility factors related to mucosal impairments in each subgroup of refractory GERD patients. In LA-A/B patients, the presence of IEM (from 0 to 1) resulted in a significant decrease of MNBI values ($\beta = -677.7$, $P = 0.024$ at 5cm and $\beta = -628.6$, $P = 0.030$ at 3cm) in both univariate and multivariate analysis (Table.2). In LA-C/D patients, IEM, absent contractility, and hypotensive EGJ-CI were significant when calculated in respective univariate analysis (all $P < 0.05$), however, only absent contractility ($P = 0.007$ at 5cm and $P = 0.002$ at 3cm) showed significance when all 3 metrics were included in multivariate analysis. The presence of absent contractility (from 0 to 1) resulted in a significant decrease of MNBI values ($\beta = -658.3$ at 5cm and $\beta = -766.1$ at 3cm) (Table.2).

In NERD patients, the presence of type III EGJ (from 0 to 1) led to a decrease of MNBI values ($\beta = -319.1$, $P = 0.014$ at 5cm) (Table.3). In BE patients, LES length and IRP were significant when calculated in respective univariate analysis (all $P < 0.05$), and only LES length showed significance ($\beta = 644.2$, $P = 0.015$ at 5cm and $\beta = 667.2$, $P = 0.005$ at 3cm) in multivariate analysis (Table.3). In other words, IEM and absent contractility were the risk factors for impaired mucosal integrity in LA-A/B and LA-C/D patients, respectively, in addition, type III EGJ and decreased LES length were the risk factors for impaired mucosal integrity in NERD and BE patients, respectively.

Discussion

This observational study aimed at comparing esophageal mucosal integrity in different subtypes of refractory GERD patients, including mild and severe EE, NERD and BE patients, as well as investigating the impact of abnormal anti-reflux barrier and esophageal body dysmotility on the mucosal integrity for the first time. Compared with FH patients, significantly decreased MNBI values were found in refractory EE, NERD and BE patients. However, the severity of macroscopic mucosal changes was not consistent with the degree of microscopic impairments reflected by baseline impedance in the distal esophagus.

Furthermore, weakened esophageal body peristalsis, type III EGJ, and shortened LES were the risk factors for the impaired mucosal integrity in EE, NERD, and BE patients, respectively. We therefore conclude that HREM and MII-pH parameters were of great value in the identification and prediction of esophageal mucosal impairments in refractory GERD patients.

DIS and reduced transepithelial resistance (TEER) could morphologically and functionally distinguish the impaired mucosal integrity in GERD patients [30–32]. Earlier in an acid perfusion experiment, BI values decreased along with DIS and correlated with esophageal TEER positively [15]. Furthermore, BI values were found to be lower in patients with pathological acid exposure than in patients with physiological acid exposure, and both were lower than in healthy people [16]. Subsequently, BI was proposed an indicator of esophageal microscopic abnormalities caused by reflux and a marker of reflux burden [14–16, 33]. FH refers to a burning sensation in the substernal region without endoscopic injury, abnormal acid exposure, and correlation between reflux events and symptoms [19]. The severity of histological impairments and the level of BI values in FH patients were comparable to those in healthy people [17, 20, 21], thus they were used as control in this study.

Decreased MNBI values to varying degrees were discovered in all groups of refractory GERD in our study. MNBI values of EE patients and NERD patients ranged from differences to no difference in previous studies [34–36]. No discrepancy in MNBI values between EE (both LA-A/B and LA-C/D) and NERD patients was found here, signifying a microscopic mucosal injury in NERD patients although no macroscopic mucosal injury at routine endoscopy. This was supported by the fact that DIS existed in NERD patients [15]. In addition, MNBI values were lower in BE patients than in control subjects, in accordance with Hemmink's research [37]. This result suggested that the esophageal region beyond Barrett's mucosa was also likely to be impaired, as MNBI was measured above Barrett's mucosa. Further research is needed to confirm the observation.

The diagnostic criteria for IEM in CCv4.0 is more strict than in CCv3.0, which contains larger proportions of ineffective or failed swallows, and fragmented peristalsis is also included in IEM in CCv4.0. In Reddy's study, the number of total reflux events (22.7% vs 9.0%, $P < 0.01$) and the bolus exposure time (3.4% vs 2.1%, $P < 0.01$) in GERD patients with more than 50% ineffective swallows were much more than those with normal motility. In addition, the total reflux events and AET increased with the increased proportion of ineffective swallows [38]. Rengarajan et al. reported that more severe dysmotility such as absent contractility was associated with abnormal reflux burden more than less severe dysmotility such as IEM [39]. The incidence of esophageal mucosal impairments increased with the increasement of reflux burden. In an HREM test of GERD patients undergoing 10 swallows, abnormal MNBI was related to $> 70\%$ ineffective swallows ($P = 0.046$), tended to be related to $> 70\%$ fragmented swallows ($P = 0.076$) and was unrelated to $\geq 50\%$ failed swallows ($P = 0.580$) [40]. Our results showed that IEM and absent contractility were the risk factor for mucosal impairments in mild and severe refractory EE patients, respectively. A decreased MNBI value was the result of abnormal reflux burden, esophageal body dysmotility and reflux clearance obstacles [29, 41, 42].

The structure and function of EGJ play an essential role in the anti-reflux barrier, and the primary mechanism is the high-pressure band between LES and CD, preventing the occurrence of reflux. It is believed that reflux burden increases with the separation between LES and CD, and the pathological morphology of EGJ (a hiatus hernia) is a predictor of abnormal acid exposure [39, 43, 44]. Consequently, it was not surprising that decreased MNBI was related with type III EGJ in NERD patients here. EGJ-CI was a new indicator of EGJ contractility and it decreased with the upgrade of EGJ morphology, EGJ contractility gradually weakened with the increase of the gap between LES and CD [25, 43]. EGJ-CI could not predict MNBI in Rogers' study but was able to predict AET in Rengarajan's study [39, 40, 44]. Our data showed that EGJ-CI was associated with MNBI at 3cm above LES in LA-C/D patients only in univariate analysis, not in multivariate analysis. We concluded that EGJ-CI has a definite influence on mucosal integrity but not as significant as EGJ morphology.

Reflux usually occurs via different mechanisms based on the anatomical and physiological variation of EGJ and LES, such as low LES pressure and transient LES relaxations [41]. Decreased LES resting pressure has been reported to be a predictor of increased acid exposure [38, 45]. IRP reflects the relaxation function of LES. Neither LES resting pressure nor IRP was significantly related to MNBI values in our study. However, we found that the decreased LES length led to decreased MNBI values in BE patients, supported by the views that shortened esophagus was related to more reflux events and higher DeMeester score [46, 47].

Limitations could not be avoided and impeded the reliability of our research, the predominant of which may be the limited sample size, but a certain number of subjects were required in regression analysis. All refractory GERD patients were recruited from only one hospital, which may lead to potential selection biases. The prevalence of BE is low and most are short-segment BE in Asia area, and thus the application of Seattle protocol is limited [48]. Only 2 biopsy samples were obtained from each patient in our study and the diagnosis of BE was likely to be inaccurate. Moreover, instead of healthy people, FH patients, whose MNBI level was comparable to healthy people, were used as a control group. Even so, our findings still had values in evaluating the characteristic of mucosal integrity impairments and in improving the therapeutic strategy for refractory GERD.

Conclusions

This study improved our understanding of the relationship between esophageal motility dysfunction and impaired mucosal integrity in refractory GERD. It showed that the impairment of esophageal mucosa in NERD patients did not differ from that of EE patients, although the degree of lesion under endoscopy differed remarkably. Hiatus hernias was likely the reason for mucosal integrity impairments in refractory NERD patients. Protective strategies on esophageal mucosa and explorations of hiatus hernias should be paid more attention to in refractory NERD patients. Abnormal esophageal body peristalsis and decreased LES length might play an important role in the impaired mucosal integrity in refractory EE and BE patients, respectively. The therapy focusing on peristaltic disorders and LES function should be considered for EE and BE patients when PPIs response is not good.

Abbreviations

GERD: gastro-oesophageal reflux disease; BI: baseline impedance; MNBI: mean nocturnal baseline impedance; EE: erosive esophagitis; NERD: non-erosive reflux disease; BE: Barrett's esophagus; FH: functional heartburn; LA: Los Angeles; LES: lower esophageal sphincter; EGJ: esophagogastric junction; PPIs: proton pump inhibitors; DIS: dilated intercellular space; HREM: high-resolution esophageal manometry; MII-pH: multichannel intraluminal impedance-pH; BMI: body mass index; CCv: Chicago Classification version; DCI: distal contractile integral; IEM: ineffective esophageal motility; IRP: integrated relaxation pressure; CD: crural diaphragm; EGJ-CI: EGJ contractile integral; AET: acid exposure time; SAP: symptom association probability; SI: symptom Index; TEER: transepithelial resistance.

Declarations

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Availability of data and materials

The data used to support the findings of this study are available from the corresponding author upon request.

Consent for publication

Not applicable.

Conflicts of Interest

The authors do not have any competing interests.

Authors' Contributions

Yu Cheng collected and analyzed the data, and wrote the manuscript. Zhijun Duan designed the study and modified the manuscript. Dong Yang, Xiaoyu Sun, Lixia Wang, Zhifeng Zhang, Wan Huang, Xiaoling Geng, Liping Su, Ping Zhang conducted the experiment. All authors approved the final version of the manuscript.

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.

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Tables

Due to technical limitations, tables 1 to 3 are only available as a download in the Supplemental Files section.

Figures

Figure 1

Typical images of esophageal dysmotility in high resolution manometric measurements. A: normal; B: ineffective esophageal motility; C: absent contractility; D: type III esophagogastric junction (EGJ); E: hypotensive EGJ contractile integral.

Figure 2

The comparison of mean nocturnal baseline impedance (MNBI) between refractory GERD and FH patients. MNBI at 5cm (A) and 3cm (B) above lower esophageal sphincter between erosive esophagitis (EE) of Los Angeles Grade (LA)-C/D, EE of LA-A/B, non-erosive reflux disease (NERD), Barrett's esophagus (BE) , and functional heartburn (FH) patients. *P < 0.005.

Supplementary Files

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