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Original Article

Esophagogastric Junction Contractility Integral Reflect the Anti-reflux Barrier Dysfunction in Patients with Gastroesophageal Reflux Disease

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Background/Aims
Anti-reflux barrier dysfunction is one of the primary mechanisms in gastroesophageal reflux disease (GERD) pathogenesis. The esophagogastric junction contractile integral (EGJ-CI) is a new metric adopted to evaluate the EGJ contractility, which implies the anti-reflux barrier function. The aim of the current study was to validate this new metric in patients with GERD and its correlation with the esophageal acid exposure, as well as the efficacy of proton pump inhibitor treatment.

Methods
Ninety-eight patients with GERD and 21 healthy controls were included in the study. Upper endoscopy, high-resolution manometry (HRM) and 24-hour multichannel intraluminal impedance-pH monitoring were performed in all patients. Three respiration cycles were chosen at the initial HRM resting frame and the value computed with distal contractile integral tool was then divided by the duration of the cycles to yield EGJ-CI. All the patients were treated with esomeprazole 20 mg twice-daily for 8 weeks.

Results
EGJ-CI was lower in the patients with GERD than that of the controls ($P < 0.05$). For patients with GERD, EGJ-CI was lower in those with hiatal hernia ($P < 0.05$). The new metric correlated with esophageal acid exposure in the supine position ($P < 0.05$), and it also negatively correlated to the total reflux episodes ($P < 0.05$). There was no significant difference on EGJ-CI between patients with and without response to the esomeprazole treatment ($P = 0.627$).

Conclusions
EGJ-CI reflected the dysfunction of the anti-reflux barrier in patients with GERD, but it had little impact on the esomeprazole response.
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Key Words
Esophagogastric junction; Gastroesophageal reflux disease; Hernia, hiatal; Manometry; Proton pump inhibitors

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Introduction

The dysfunction of the anti-reflux barrier is one of the primary mechanisms in the pathogenesis of gastroesophageal reflux disease (GERD). The esophagogastric junction (EGJ) plays an important role in the anti-reflux barrier. The components of EGJ are complex, mainly includes lower esophageal sphincter (LES), crural diaphragm (CD), His angle and flap valve. Among them, LES and CD are especially crucial in this anti-reflux function.

The high-resolution manometry (HRM) has the advantage of fine fidelity on presenting esophageal motility and assessing EGJ function. Using the esophageal pressure topography, HRM can synchronously present the peristalsis of the whole esophagus, thus the EGJ can be distinguished more accurately.[1,2] Integrated relaxation pressure (IRP), expiratory EGJ pressure (EGJP-exp), and inspiratory EGJ pressure (EGJP-insp) are the metrics commonly used to evaluate the anti-reflux barrier function,[3,4] but all of them have some shortcomings. IRP indicates the nadir EGJ pressure after deglutition and helps to exclude the outflow obstruction in EGJ. EGJP-insp represents the EGJ contraction during inspiration, and EGJP-exp represents the resting LES pressure during expiration when the diaphragm is relaxed. Thus none of the above parameters fully describes the overall EGJ contractility. In fact, the competence of the anti-reflux barrier depends a lot on the contractility of EGJ at rest which could not be predicted by the previous metrics. So it is necessary to develop some new metrics to quantify the barrier function at rest.

Recently a new parameter, EGJ contractile integral (EGJ-CI) was developed by Nicodème et al[4] to evaluate the EGJ function. Three respiration cycles in the initial frame without swallowing or belching were chosen, the value computed with the distal contractile integral (DCI) tool was then divided by the duration of the cycles to yield the new parameter. By integrating the contraction length and vigor of the barrier, as well as excluding the influence of respiration rate, EGJ-CI may be superior to the conventional parameters, which only take the pressure into consideration. However, this new parameter has not been validated in the patient cohort. Gor et al[5] found that lower EGJ-CI was associated with better symptom response to antireflux surgery. But whether EGJ-CI could impose some indication on the efficacy of proton pump inhibitor (PPI) treatment has not been investigated. Thus the aims of this study were to assess whether the EGJ-CI can help to identify the dysfunction of anti-reflux barrier in patients with GERD, to explore whether it would affect the symptom response to the PPI treatment.

Materials and Methods

Subjects

Consecutive outpatients who had heartburn and/or regurgitation as their main complaint were enrolled. The patient's symptom should last for at least 3 months, and more than 2 days in one week. The severity of the symptoms should be at least moderate (mild: symptom could be tolerated and has little impact on patients' sleep; moderate: daily life and sleep were affected substantially; severe: patients unable to have normal activities due to symptoms). All patients underwent endoscopy in the first affiliated hospital of Sun Yat-Sen university, Guangzhou, China which was performed by the same physician. Patients would be also excluded if they had the following: previous esophageal or gastrointestinal surgery, peptic ulcer, gastrointestinal tumor, primary or secondary severe esophageal motility disorders, and severe cardiac, renal or pulmonary disease. Another 21 volunteers without digestive symptoms, systemic disorders or major abdominal surgery were recruited as healthy controls.

All the patients received esomeprazole 20 mg twice-daily treatment for 8 weeks.[6,7] Esomeprazole therapy was defined as effective if the patients had less than one episode of mild reflux symptoms during the last week of therapy, otherwise esomeprazole therapy was considered a failure. For erosive esophagitis (EE) patients, if the mucosal erosion does not heal on the final week of esomeprazole therapy despite symptom relief, the treatment was also considered a failure.

The protocol was approved by the Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University. Written informed consent was obtained from all individuals before every procedure.

High-resolution Manometry

HRM was performed in all subjects in the supine position after fasting for at least 8 hours. The HRM catheter was assembled with 36 circumferential sensors separated at 1-cm intervals (Given Imaging, Duluth, GA, USA). Transducers were calibrated at 0 and 300 mmHg using externally applied pressure. The catheter was placed transnasally with at least 3 sensors in the stomach and the changes of pressure from the upper esophageal sphincter to the stomach were recorded. The manometric protocol included a 30-second baseline recording and ten 5 mL liquid swallows. The studies were analyzed manually through using the Manoview software (Given Imaging, Duluth, GA, USA).

The esophageal pressure topography metrics defined in the updated Chicago classification were measured including IRP, EGJ-CI, EGJP-exp, and EGJP-insp.[8]

When the EGJ-DCI was measured, the influence of the diaphragm was excluded if the distance of LES and CD is more than 2 cm as shown by HRM.[9] The measurement of EGJ-DCI is shown in Figure 1.

EGJP-insp was defined as the average maximal inspiratory EGJ pressure and EGJP-exp was the average EGJ pressure midway between inspirations for the same 3 respiratory cycles chosen to calculate the EGJ-DCI in the baseline without swallow.

Twenty-four-hour Multichannel Intraluminal Impedance-pH Monitoring

All subjects underwent 24-hour monitoring by using an ambulatory MII-pH monitoring system (Sleuth; Sandhill Scientific, Inc; Highland Ranch, CO, USA). The pH electrode was placed at 5 cm above the upper margin of the LES, and impedance were recorded at 6 sites (3, 5, 7, 9, 15, and 17 cm above the LES, respectively). The meal time was excluded from the analysis.

All patients with GERD were divided into 3 groups in the study: EE determined by upper endoscopy, non-erosive reflux disease (NERD) with abnormal esophageal acid exposure (acid exposure time [AET] $\geq$ 4%), and hypersensitive esophagus (AET $<$ 4% and symptom association probability $\geq$ 95%).

Statistical Methods

All data were presented as median (interquartile range). Rank sum test was used for comparison among groups. Spearman rank correlation was used to explore the correlation between EGJ-CI and other parameters. The *P*-value less than 0.05 were considered statistically significant. Statistical analysis was completed by using SPSS 20.0 (SPSS Inc, Chicago, IL, USA).

Results

Demographic Characteristics of Patients with Gastroesophageal Reflux Disease

A total of 134 patients with heartburn and/or regurgitation as their main complaint were screened. Thirteen patients were excluded after upper endoscopy due to the active peptic ulcer. Then 23 patients inconsistent with the criteria of GERD on 24-hour MII-pH monitoring were excluded. Finally, 39 EE patients, 38 NERD patients with abnormal esophageal acid exposure, 21 patients with hypersensitive esophagus, and 21 healthy controls were included in the analysis (Table 1). Eleven patients with GERD were found to have a hiatal hernia under upper endoscopy.

Comparison of High-resolution Manometry Findings Between Patients with Gastroesophageal Reflux Disease and Healthy Controls

Though the distal latency (DL) values of all GERD groups were similar with healthy controls, it was longer in NERD patients with hypersensitive esophagus when compared to that of EE patients ($P < 0.05$) (Table 2). There were no significant differences

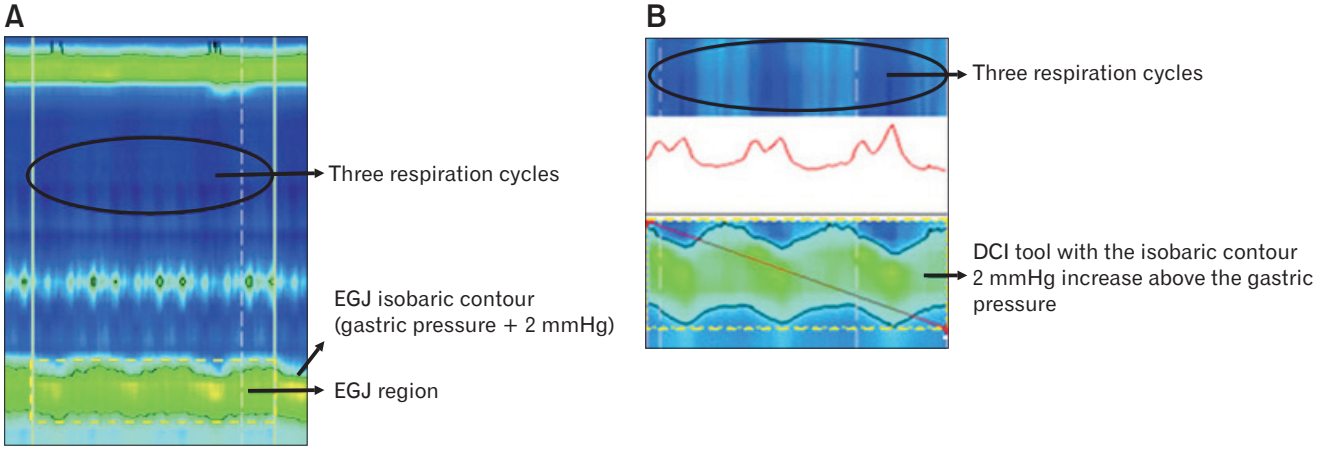

Figure 1. The calculation of esophagogastric junction distal contractile integral (EGJ-DCI). Three respiration cycles beginning at the inspiration are chosed by adding a swallow frame at baseline state. Using the isobaric contour, the barrier margins are setup at a pressure with 2 mmHg higher than the intragastric pressure. Then the value of EGJ-DCI can be obtained by using the DCI tool. (A) Changes of total esophageal pressure at rest and the yellow box shows region chose to calculate EGJ-DCI. (B) Calculation of EGJ-DCI using DCI tool.

Table 1. Demographic Data of Patients with Gastroesophageal Reflux Disease and Controls

	EE (n = 39)	NERD with pathological acid reflux (n = 38)	Hypersensitive esophagus (n = 21)	Control (n = 21)
BMI (kg/m^2)	24.00 ± 3.05	23.24 ± 2.95	23.14 ± 3.89	20.11 ± 1.86
Male	27	21	10	8
Age (yr)	51 (38, 65)	46 (36, 54)	44 (34, 59)	25 (24, 27)

EE, erosive esophagitis; NERD, non-erosive reflux disease; BMI, body mass index.
BMI were expressed as median ± SD and age were expressed as medians (interquartile range).

Table 2. Comparisons of Conventional High-resolution Manometry Metrics Between Patients with Gastroesophageal Reflux Disease and Controls

	EE (n = 39)	NERD with pathological acid reflux (n = 38)	Hypersensitive esophagus (n = 21)	Control (n = 21)	*P*-value
Median IRP (mmHg)	8.20 (6.00, 1.80)	8.83 (5.85, 11.01)	9.90 (6.95, 12.50)	8.20 (6.00, 11.80)	0.097
DL (sec)	5.80 (5.40, 6.50)	6.00 (5.38, 6.60)	6.50 (5.95, 6.50)	6.10 (5.80, 6.65)	0.015
DCI (mmHg·cm·sec)	773.08 (242.26, 1248.62)	756.22 (356.19, 1366.74)	715.40 (424.31, 1274.05)	1422.91 (1219.64, 2232.45)	0.001

EE, erosive esophagitis; NERD, non-erosive reflux disease; IRP, integrated relaxation pressure; DL, distal latency; DCI, distal contractile integral.
All the values were expressed as medians (interquartile range).

Table 3. Comparisons of 3 Esophagogastric Junction Metrics Between Patients with Gastroesophageal Reflux Disease and Controls

	EE (n = 39)	NERD with pathological acid reflux (n = 38)	Hypersensitive esophagus (n = 21)	Control (n = 21)	*P*-value
EGJ-CI	22.08[a] (19.50, 31.47)	26.21[a] (15.49, 37.75)	29.83[a] (19.39, 44.38)	62.58 (37.73, 83.30)	< 0.01
EGJP-insp (mmHg)	16 (10.00, 21.00)[a]	16 (12.00, 24.25)[a]	21 (15.50, 25.50)	29 (21.00, 32.50)	< 0.01
EGJP-exp (mmHg)	9 (4.00, 15.00)[a]	10 (4.50, 16.25)[a]	13 (6.50, 17.00)	17 (13.00, 26.00)	< 0.01

[a]Different from control.
EE, erosive esophagitis; NERD, non-erosive reflux disease; EGJ-CI, esophagogastric junction contractile integral; EGJP-insp, inspiratory EGJ pressure; EGJP-exp, expiratory EGJ pressure.
All the values were expressed as medians (interquartile range). $P < 0.01$ indicated that the results of all the groups was not similar. Then the specific difference between each 2 groups would be compared.

on the IRP values between patients with GERD and the controls ($P > 0.05$). The DCI decreased in all GERD groups when compared to that of healthy controls ($P < 0.05$), but the differences were not significant within all GERD groups ($P > 0.05$) (Table 2).

The EGJP-insp, EGJP-exp, and EGJ-CI values of EE patients and NERD patients with pathological acid reflux were lower than that of the healthy controls ($P < 0.05$). However, only the EGJ-CI in patients with hypersensitive esophagus was lower than that of healthy controls ($P < 0.05$). The differences of 3 HRM metrics within all GERD groups were not significant ($P > 0.05$) (Table 3).

Both the EGJP-insp and EGJP-exp in patients with GERD with hiatal hernia was similar with those without (18 [7, 26] mmHg vs 17 [13, 24] mmHg, 8 [2, 16] mmHg vs 11 [5, 15] mmHg; $P > 0.05$). However, the EGJ-CI in patients with GERD with hiatal hernia was lower than those without (19.80 [16.99, 20.63] mmHg vs 28.00 [18.62, 39.13] mmHg, $P < 0.05$).

Correlation Between Esophagogastric Junction Contractile Integral and Other Metrics

EGJ-CI correlated with the conventional pressure metrics of IRP, EGJP-insp, and EGJP-exp positively ($P < 0.05$).

EGJ-CI correlated with esophageal acid exposure in supine position ($P < 0.05$) negatively, and it correlated to the total reflux episodes negatively ($P < 0.05$). These results are shown in Figure 2.

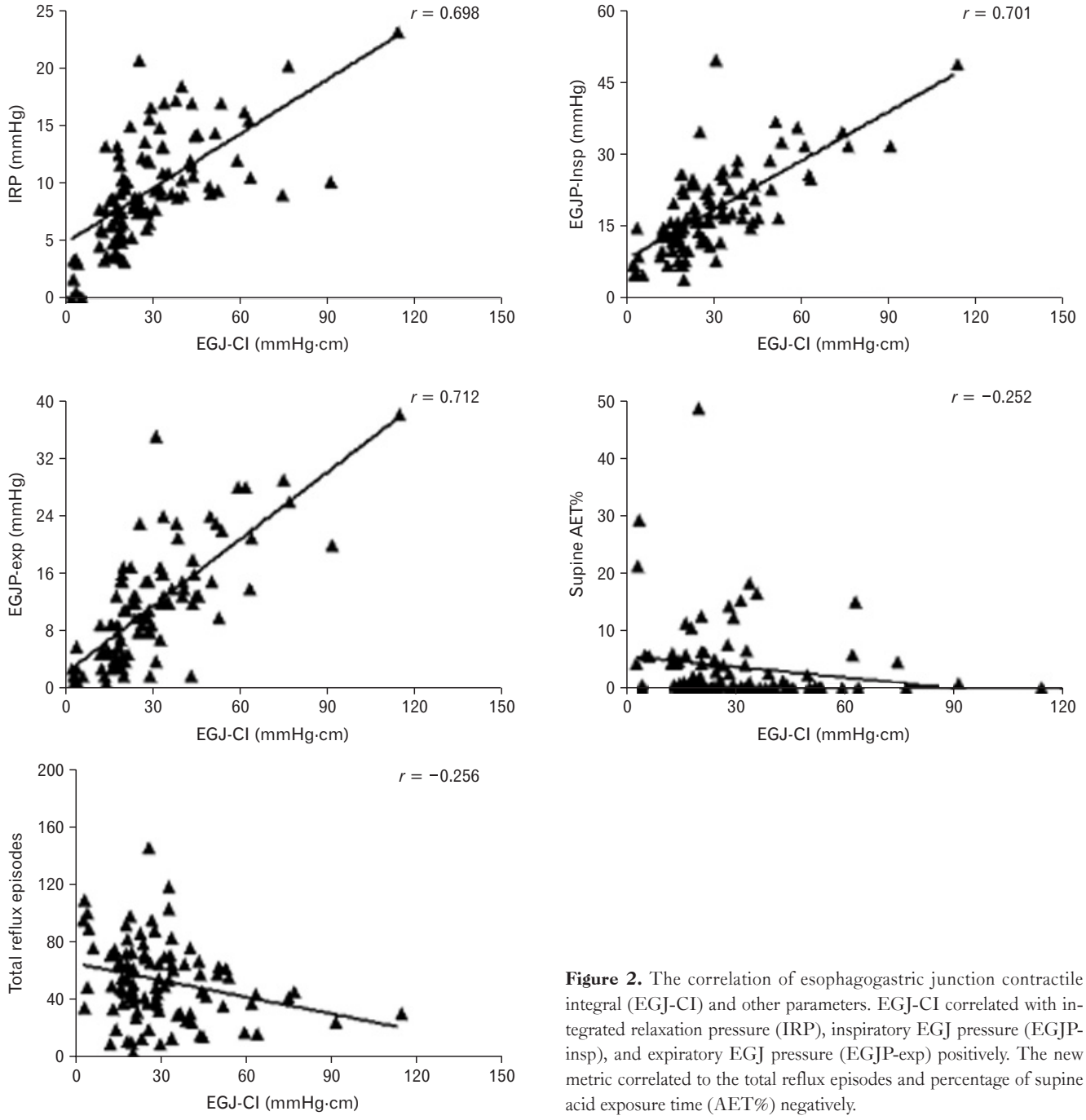

Figure 2. The correlation of esophagogastric junction contractile integral (EGJ-CI) and other parameters. EGJ-CI correlated with integrated relaxation pressure (IRP), inspiratory EGJ pressure (EGJP-insp), and expiratory EGJ pressure (EGJP-exp) positively. The new metric correlated to the total reflux episodes and percentage of supine acid exposure time (AET%) negatively.

Relationship Between the Esophagogastric Junction Contractile Integral and the Efficacy of Esomeprazole

Eighty-three patients finished the 8-week therapy. The esomeprazole therapy was effective in 67 patients while failured in 16 patients. The percentage of EE patients was similar between the 2 groups ($P > 0.05$). We compared the differences on reflux patterns and HRM metrics between the 2 groups, and the results are shown in Table 4. The percentage of AET (AET%) was higher in the PPI responder group ($P < 0.05$). The EGJ-CI was 24.35 (16.99-33.15) mmHg·cm in the esomeprazole responder group, and 25.78 (14.77-44.84) mmHg·cm in the esomeprazole non-responders. The difference was not significant ($P = 0.627$). The other parameters were similar between the 2 groups ($P > 0.05$).

Table 4. Comparisons of Reflux Patterns and High-resolution Manometry Metrics Between Proton Pump Inhibitor Effective and No Effective Group

	PPI responders (n = 67)	PPI non-responders (n = 16)	*P*-value
EE patients	30 (44.8%)	6 (37.5%)	0.598
AET%	4.90 (1.30, 10.10)	1.90 (0.40, 4.70)	0.015
Total reflux episodes	55.66 ± 21.37	59.36 ± 41.60	0.780
EGJ-CI (mmHg·cm)	24.35 (16.99, 33.15)	25.78 (14.77, 44.84)	0.627
EGJP-insp (mmHg)	16 (11, 23)	15 (12, 24)	0.804
EGJP-exp (mmHg)	9 (3, 15)	7 (4, 18)	0.992
Median IRP (mmHg)	8.84 ± 4.77	10.68 ± 6.11	0.279
DCI (mmHg·cm·sec)	774.47 (368.01, 1568.53)	908.33 (682.28, 1045.10)	0.820

PPI, proton pump inhibitor; EE, erosive esophagitis; AET%, percentage of acid exposure time; EGJ-CI, esophagogastric junction contractile integral; EGJP-insp, inspiratory EGJ pressure; EGJP-exp, expiratory EGJ pressure; IRP, integrated relaxation pressure; DCI, distal contractile integral.
Total reflux episodes and median IRP were expressed as median ± SD, the other values were expressed as medians (interquartile range).

Discussion

The anti-reflux barrier plays an important role and which is comprised of LES and the CD which is identified as the distal high pressure zone in conventional esophageal manometry.[10] The HRM, a manometric technology in which the esophageal pressure is displayed topographically, has the advantage to better identify the anatomic structure and pressure changes of EGJ. For example, HRM has similar sensitivity but higher specificity in the detection of hiatal hernias than endoscopy.[11] Recently, the appropriate parameter, EGJ-CI, has become to accurately evaluate the status of EGJ at rest in the Chicago classification. Although it has been proved in a study by Nicodème et al[4] that this parameters is useful in refractory GERD patients to clarify the underlying mechanism of lack of good response to PPI, this parameters has not been validated in the outcome study. So we used this new parameter EGJ-CI to assess the function of the anti-reflux barrier in patients with GERD, and try to find out its correlation with esophageal acid exposure, as well as the efficacy of PPI treatment. It turned out that the EGJ-CI was useful in identifying patients with GERD from the healthy population. This parameter negatively correlated with esophageal acid exposure in the supine position and the total reflux episodes.

Currently there are some metrics commonly used to evaluate the EGJ function. IRP measurement is the fundamental calculation of the Chicago classfication,[3] which indicates the adequacy of deglutitive relaxation. EGJP-insp and EGJP-exp represent the barrier pressure at the respiration cycle separately. Although commonly used, none of these parameters is able to delineate the comprehensive contractility of EGJ without interference of respiration at rest. The new metric EGJ-CI represents the overall EGJ contractility of 3 respiration cycles. It captures more factors attributing to the barrier function. The positive correlations between EGJ-CI and 3 conventional parameters showed that using EGJ-CI to evaluate the function of anti-reflux barrier is feasible.

EGJ-CI incorporated both LES and diaphragm contraction and we found that the EGJ-CI was lower in all GERD subgroups when compared to that of the volunteers. Tolone et al[12] reported that defective EGJ-CI was more frequently found in patients with GERD than in patients with functional heartburn, but they did not compare the differences between patients with GERD and healthy controls. Nicodème et al[4] divided the patients with GERD into 3 groups and reported that only the patients that fulfilled all the criteria of GERD had lower EGJ-CI, which was in line with our results. We also found that when compared EGJP-insp, EGJP-exp, and EGJ-CI between patients with and without hiatal hernia, only the difference of EGJ-CI was significant. These results suggested that the new metric was useful in identifying the dysfunction of EGJ barrier in patients with GERD.

No cut-off value could be obtained concerning the EGJP-insp, EGJP-exp, and EGJ-CI through our study to distinguish patients with GERD from controls. Thus the EGJ dysfunction might not be the unique factor for GERD. Although DL was shorter within EE patients, considering none of the EE patients had DL for less than 4.2 seconds, this might not be a characteristic motility feature for EE patients.

Gor et al[5,9] reported that both EGJ-DCI and EGJ-CI measurements were useful in assessing the possibility of pathological acid reflux. They defined a cut-off value of 39.3 mmHg·cm for EGJ-CI as the critical value, but the sensitivity and specificity were

not satisfactory. EGJ-CI correlated to the reflux episodes in our study. This result supported that the dysfunction of anti-reflux barrier contributes to reflux. However, the new metric correlated with esophageal acid exposure only in the supine position. This might be due to the lack of gravity effect in the supine position for the reflux component, then the anti-reflux barrier became the most important protection from the reflux.

Both EGJ-CI and EGJ-DCI were reported to be useful in predicting the symptom response after antireflux surgery.[5,9] But the predictive value of these new metrics on the efficacy of medical therapy was poor. In our study, the PPI treatment was effective in patients with higher AET%. Although the EGJ-CI seemed higher in patients with poor response to esomeprazole treatment, the difference was not significant. This might due to the fact the PPI acts on the acid secretion, instead of on the anti-reflux barrier function directly.

There are some limitations in our study. Firstly, the patients with "functional heartburn" were not included in the research. We believed that the data of these patients could be another evidence of anti-reflux barrier dysfunction in patients with GERD, and the comparison of EGJ-CI between NERD and functional heartburn patients would be useful in revealing the different pathogenesis of these diseases in further research. Secondly, there were lack of data on the effect of PPI therapy to EGJ-CI, which could reflect the primary nature of decreased EGJ-CI in the pathogenesis of GERD.

In summary, our findings in the study suggest that the new HRM metric EGJ-CI could be used in identifying the dysfunction of anti-reflux barrier in patients with GERD. Future research is needed to evaluate whether it is useful in predicting the outcome of anti-reflux surgery.

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Conflicts of interest: None.

Author contributions: Chenxi Xie and Jinhui Wang: study concept, acquisition of data, analysis, drafting, and study supervision; Yuwen Li, Niandi Tan, and Yi Cui: acquisition of data and analysis; and Minhu Chen and Yinglian Xiao: study concept, acquisition of data, analysis, drafting, study supervision, and finalizing the manuscript.

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