Original Article

The Usefulness of the Measurement of Esophagogastric Junction Distensibility by EndoFLIP in the Diagnosis of Gastroesophageal Reflux Disease

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Background/Aims: Increased esophagogastric junction (EGJ) relaxation is the most important mechanism involved in gastroesophageal reflux disease (GERD). An endoscopic functional luminal imaging probe (EndoFLIP®) is a device used to quantify EGJ distensibility in routine endoscopy. The aim of the current study was to assess the usefulness of EndoFLIP® for the diagnosis of GERD compared to normal controls.

Methods: We analyzed EndoFLIP® data from 204 patients with erosive reflux disease (ERD), 310 patients with nonerosive reflux disease (NERD), and 277 normal subjects. EndoFLIP® uses impedance planimetry to measure 16 cross-sectional areas (CSAs) in conjunction with the corresponding intrabag pressure within a 4.6 cm cylindrical segment of a fluid-filled bag. The EGJ distensibility was assessed using 40 mL volume-controlled distensions.

Results: The mean distensibility index values were 13.98 mm^2/mm Hg in ERD patients, 11.42 mm^2/mm Hg in NERD patients, and 9.1 mm^2/mm Hg in normal subjects. There were significant differences in EGJ distensibility among the three groups (p<0.001). In addition, the CSAs were significantly higher in the ERD (291.03±160.77 mm^2) and NERD groups (285.87±155.47 mm^2) than in the control group (249.78±144.76 mm^2, p=0.004). We determined the distensibility index cutoff value of EGJ as 10.95 for the diagnosis of GERD by receiver operating characteristic curve analysis.

Conclusions: The EGJ distensibilities of GERD patients were higher than those of normal subjects, regardless of the presence of reflux esophagitis. Thus, the measurement of EGJ distensibility using the EndoFLIP® system could be useful in the diagnosis of GERD. **(Gut Liver 2021;15:546-552)**

Key Words: Gastroesophageal reflux disease; Esophagogastric junction; Functional lumen imaging probe

INTRODUCTION

Gastroesophageal reflux disease (GERD), including acid reflux and heartburn, is common worldwide.[1] It is classified as erosive reflux disease (ERD) in the esophagus, and nonerosive reflux disease (NERD) without esophageal mucosal abnormality, but with symptoms such as heartburn.[2,3] Increased esophagogastric junction (EGJ) relaxation is the most important pathophysiology of GERD.[4] Endoscopy, high-resolution manometry, and 24-hour ambulatory pH monitoring all have limitations when it comes to evaluating the function of the EGJ.[5,6]

The endoscopic functional luminal imaging probe (EndoFLIP®) is a medical device designed to evaluate the distensibility of the EGJ, and has been widely used for measuring esophageal functional disease in Western countries.[7,8] Since the pathology of GERD involves reflux occurring when the distensibility of the EGJ increases,

EndoFLIP[®] is useful in the diagnosis of GERD.[9,10] A previous small-population study showed that EndoFLIP[®] helps to evaluate GERD by evaluating the function of the EGJ.[8] However, another study demonstrated controversies surrounding the usefulness of EndoFLIP[®] in GERD patients.[11]

In this study, we aimed to evaluate the clinical usefulness of the measurement of EGJ distensibility using EndoFLIP[®] in a large population including patients with GERD compared to control patients.

MATERIALS AND METHODS

1. Study design

This single-center prospective study was performed in the Department of Gastroenterology and Digestive Endoscopy at the CHA Bundang Medical Center (Seongnam, Korea) from March 2016 to October 2018. All patients provided written informed consent, and the study was approved by the Institutional Review Board of the CHA Bundang Medical Center (IRB number: CHAMC 2016-04-016-013).

2. Patients

Individuals between 20 and 79 years of age, with typical reflux-related symptoms such as heartburn and regurgitation, and scheduled to undergo a screening gastroscopy and EndoFLIP[®] imaging before taking anti-acid medication, were included as GERD group in this study. Additionally, according to the results, patients with erosive esophagitis, as determined by gastroscopy, were referred to as the ERD group. Patients with no erosive esophagitis, but with typical reflux symptom and positive response to proton pump inhibitors were classified as the NERD group.[12] Control group was defined as participants having nonspecific abdominal symptom, but without any typical reflux symptoms and demonstrating normal 24-hour ambulatory pH monitoring.

Patients were excluded for the following reasons: (1) inability to receive a gastroscopy or EndoFLIP[®] imaging; (2) inability to provide informed consent; (3) hemodynamic instability (systolic blood pressure <90 mm Hg), or if the peripheral oxygen saturation (SpO_2) was 90% in room air, or <95% on 2 L/min of oxygen at baseline before the procedure; (4) psychological problems; (5) acute severe infection; and (6) evidence of esophageal motility disorder on esophageal manometry.

3. Endoluminal functional lumen imaging probe

EndoFLIP[®] is a device used to measure EGJ distensibility. The catheter (EF-325) had a total length of 240 cm and an outer diameter of 3 mm. The EndoFLIP[®] catheter, with 16 paired impedance electrodes and a pressure sensor, had a complaint bag at the distal end that was able to extend to 40 mL in volume.[13] The bag was filled with the conduct medium, and the impedance electrodes were able to measure the cross-sectional area (CSA) and the response of the pressure to the increased area, defined as the distensibility. When the catheter is placed in the EGJ with the gastroscope, the activated electrodes face each other, allowing the CSA to be measured in the range of 10 to 450 mm^2.[14,15]

4. Protocol

All patients with any abdominal symptoms underwent gastroscopy, ambulatory pH monitoring, high-resolution manometry, and EndoFLIP[®]. We conducted the studies as following order: (1) gastroscopy, (2) EndoFLIP[®], (3) high-resolution manometry, or (4) 24-hour monitoring on the same day. The catheter of 24-hour monitoring was removed the next day. Patients with GERD grade LA classification A to D, as determined by gastroscopy, were classified into the ERD group.[16] In addition, among the patients without erosion, determined by gastroscopy, patients with typical reflux symptom and response to proton pump inhibitors regardless of the results 24-hour ambulatory pH monitoring were classified as the NERD group. Patients who did not meet either the ERD or NERD criteria following both gastroscopy and 24-hour ambulatory pH monitoring, and showed normal findings, but having nonspecific abdominal symptoms were classified as the control group.

The primary outcome was the CSA and distensibility index (mm^2/mm Hg) measured using EndoFLIP[®]. The measurement was taken by a physician (I.K.Y) by filling the EndoFLIP[®] catheter with 40 mL of saline and obtaining the average of three measurements.

5. Statistical analysis

Continuous variables are expressed as means±standard deviations, and discontinuous variables are expressed as counts and percentages. SPSS version 24.0 for Windows (IBM Corp., Armonk, NY, USA) was used for data entry and statistical analyses. For analyses between the groups, analysis of variance was used to compare continuous variables as appropriate, and either the chi-square test or Fisher exact test was used for categorical data. The empirical receiver operating characteristic curve, which is a plot of true positive rate versus false positive rate for all possible cutoff values, was used. Any p-values <0.05 were considered statistically significant.

RESULTS

1. Baseline characteristics

Initially, 862 patients were assessed; among them, 49 patients were excluded because they were unable to undergo gastroscopy or EndoFLIP® and had evidence of abnormal esophageal motility disorder following esophageal manometry (n=13), hemodynamic instability during the procedure (n=5), severe infection (n=3), or psychological problems (n=1) (Fig. 1). In total, 791 patients (ERD, 204; NERD, 310; control, 277) were included in the final analysis. Across the three groups, the baseline characteristics were not significantly different in terms of age, sex, body mass index, or GERD-Q score (Table 1). Furthermore, the ERD group (6.33±8.72 years) had a significantly longer duration of symptoms compared to the other groups (NERD group, 3.24±4.04 years; control group, 4.86±5.71 years; p=0.021). In the ERD group, the LA classifications A, B, C, and D of patients were 113 (55%), 63 (31%), 27 (13%), and one (1%), respectively.

2. Assessment of distensibility index and CSA using EndoFLIP®

Fig. 2 shows the typical images of EndoFLIP® in the ERD and control patient. The distensibility index, measured using EndoFLIP®, was significantly higher in the ERD (13.98 ± 11.54 mm^2/mm Hg) and NERD (11.42 ± 9.62 mm^2/mm Hg) groups than in the control group (9.10 ± 7.23 mm^2/mm Hg, $p<0.001$) (Fig. 3). In addition, the CSA was also significantly higher in the ERD (291.03 ± 160.77 mm^2) and NERD (285.87 ± 155.47 mm^2) groups than in the control group (249.78 ± 144.76 mm^2, $p=0.004$) (Table 2).

In high-resolution manometry, the integrated relaxation pressure was significantly lower in the ERD group than in the other groups (10.19 ± 6.84 mm Hg, $p=0.023$). In the 24-hour ambulatory pH monitoring, both the ERD and NERD groups had a significantly higher number of reflux episodes ($p=0.044$), including the number of acid reflux episodes ($p=0.023$) and nonacid reflux episodes ($p=0.021$), and DeMeester scores ($p<0.001$).

3. Assessment of the optimal distensibility index cutoff value

We determined the distensibility index cutoff value of
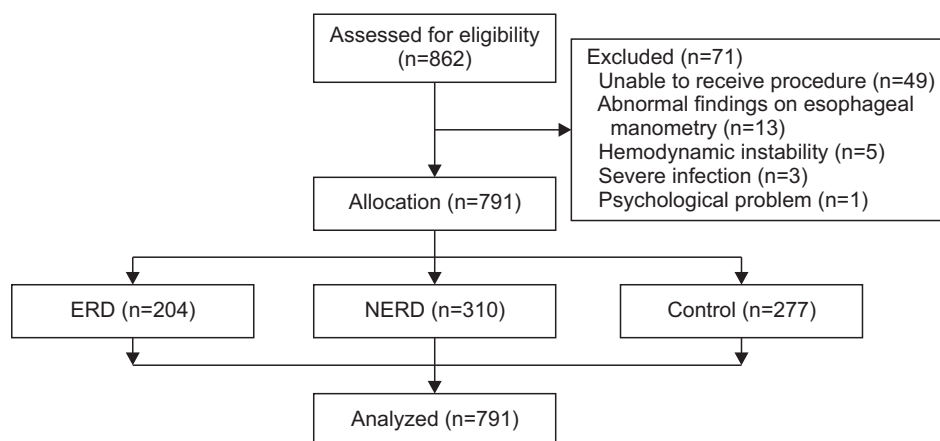
Fig. 1. Assembly of patients. Flowchart showing the recruitment of study patients.
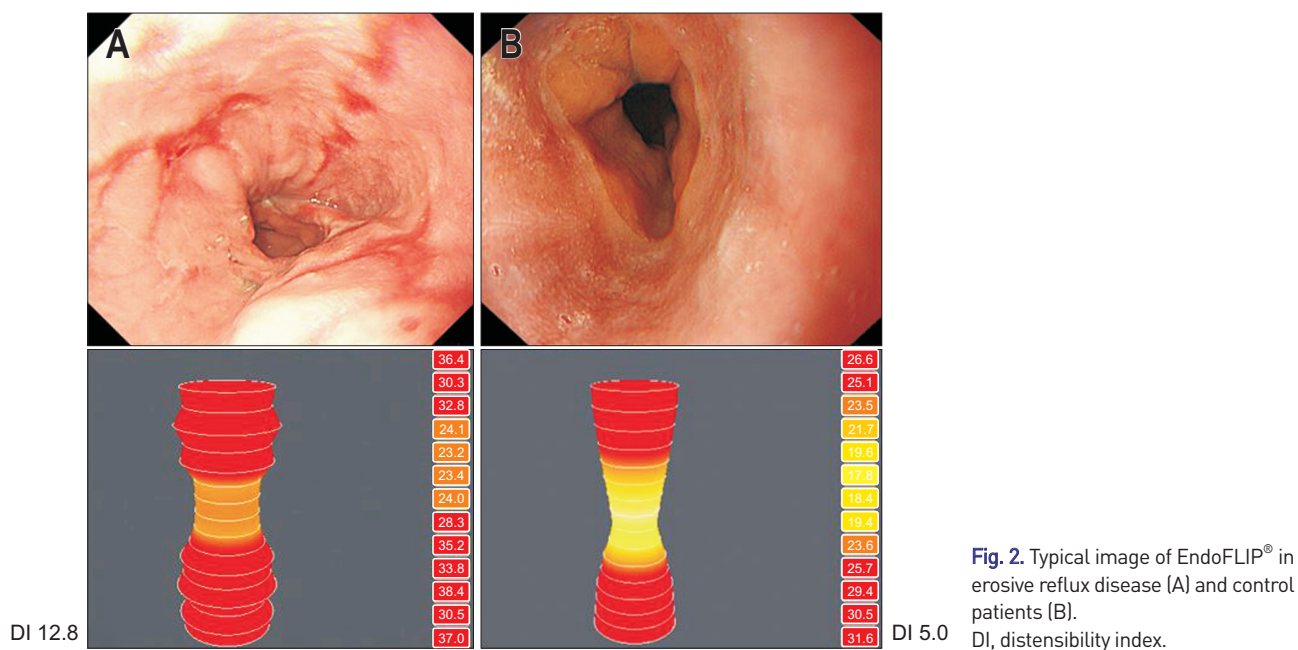ERD, erosive reflux disease; NERD, nonerosive reflux disease.

Table 1. Baseline Characteristics

| Variable	ERD (n=204)	NERD (n=310)	Control (n=277)	p-value
Age, yr	46.53±14.50	46.93±14.42	49.14±15.39	0.239*
Sex (male:female)	118:86	151:159	140:137	0.121[†]
BMI, kg/m^2	22.56±3.54	22.60±3.63	22.31±2.78	0.838*
Height, cm	165.70±10.41	163.62±8.56	164.76±10.02	0.326*
Weight, kg	62.69±14.77	61.10±12.37	61.09±11.67	0.678*
Duration of symptom, yr	6.33±8.72	3.24±4.04	4.86±5.71	0.021*
GERD-Q score	8.26±2.99	8.49±3.00	8.19±2.72	0.772*
LA classification, A/B/C/D	113 (55)/63 (31)/27 (13)/1 (1)			

Data are presented as mean±SD or number (%).
ERD, erosive reflux disease; NERD, nonerosive reflux disease; BMI, body mass index; GERD-Q, gastroesophageal reflux disease questionnaire.
Statistical significance between groups was tested by *analysis of variance, [†]chi-square analysis.

Fig. 2. Typical image of EndoFLIP® in erosive reflux disease (A) and control patients (B).
DI, distensibility index.
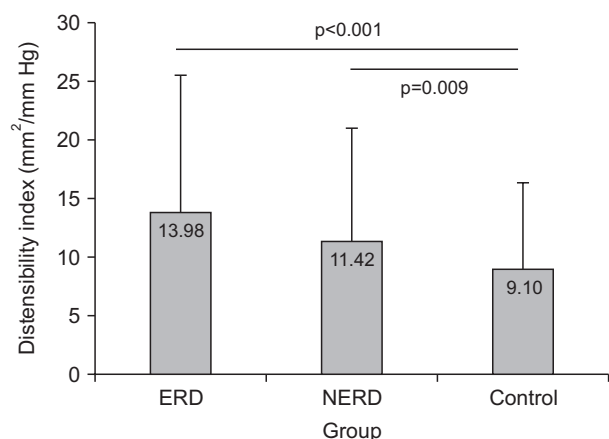
Fig. 3. Distensibility index for the gastroesophageal reflux disease group and controls. The distensibility index, measured by EndoFLIP®, was significantly higher in the erosive reflux disease (ERD) group and nonerosive reflux disease (NERD) group than in the control group (p<0.001).

the EGJ for GERD diagnosis by receiver operating characteristic curve analysis; the area under the curve was 0.610 (95% confidence interval, 0.569 to 0.650; p=0.021) (Fig. 4). Considering the sensitivity (0.432) and specificity (0.743), we determined the distensibility index cutoff value to be 10.95.

DISCUSSION

GERD is a disease that causes the reflux of gastric acid or food into the esophagus and leads to associated symp-toms.[2,17] In Western Europe and North America, the proportion of individuals experiencing GERD at least once a week is as high as 20% to 30% of the population.[3] GERD is classified as ERD or NERD without the presence of esophageal mucosal abnormalities, but with symptoms such as heartburn,[18] and can progress to Barrett's esophagus if neglected. GERD is one of the main causes of diseases such as esophageal ulceration, esophageal stricture, and tumors, and it can rapidly decrease the quality of life of patients.[19]

EndoFLIP® is a device that can be used to measure the function of the EGJ and help to diagnose many esophageal functional diseases, such as achalasia.[11] It can measure the distensibility, compliance, diameter, and CSA of the EGJ in real time, and thus help in assessing the function of the EGJ.[11,20] Although endoscopy, high-resolution manometry, and 24-hour ambulatory pH monitoring are all helpful in diagnosing GERD, they have limitations when it comes to measuring the function of the EGJ.[8] Measuring the distensibility of the EGJ in accordance with the pathophysiology of increasing reflux when the distensibility of the EGJ increases in GERD patients can assist in the diagnosis of GERD.[6,7] Unlike the barostat, this method does not require fluoroscopy and has the advantage of being able to assess images quickly in real-time.[7]

However, the usefulness of EndoFLIP® in the diagnosis of GERD is controversial.[8,11] Kwiatek *et al.*[8] investigated the usefulness of EndoFLIP® in the diagnosis of GERD, confirming that CSA and distensibility were significant parameters. However, only a small number of individuals, 20 patients and 20 controls, were studied. On the other hand, Tucker *et al.*[11] demonstrated that the use of EndoFLIP® to

Table 2. Comparison of EndoFLIP® with High-Resolution Manometry and 24-Hour pH Ambulatory

Characteristic	ERD (n=204)	NERD (n=310)	Control (n=277)	p-value
Distensibility index, mm^2/mm Hg	13.98±11.54	11.42±9.62	9.10±7.23	<0.001
Cross-sectional area, mm^2	291.03±160.77	285.87±155.47	249.78±144.76	0.004
High-resolution manometry				
IRP, mm Hg	10.19±6.84	12.37±8.13	12.64±7.92	0.023
24-Hour ambulatory pH monitoring				
All reflux episodes	56.36±39.41	53.31±38.59	41.31±24.01	0.044
Acid reflux episodes	19.72±21.60	20.99±24.99	14.57±14.00	0.023
Nonacid reflux episodes	35.25±28.66	32.19±25.03	26.93±17.73	0.021
DeMeester score	7.88±10.70	7.38±13.59	3.20±4.61	<0.001

Data are presented as mean±SD.
ERD, erosive reflux disease; NERD, nonerosive reflux disease; IRP, integrated relaxation pressure.
Statistical significance between groups was tested by analysis of variance.
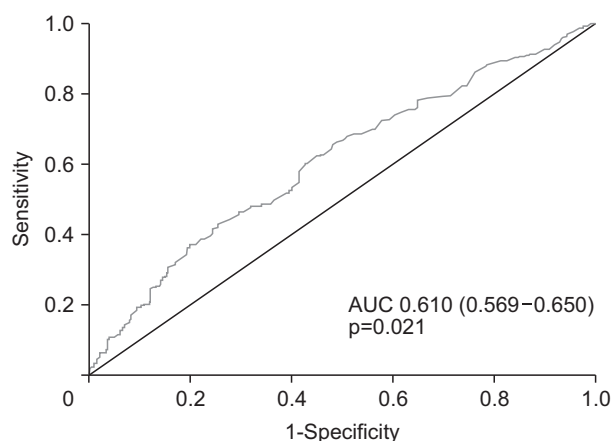
Fig. 4. Optimal distensibility index cutoff value. Receiver operating characteristic curve analysis showing the optimal distensibility index cutoff value. Cutoff value=10.95, with sensitivity (0.432) and specificity (0.743).
AUC, area under the curve.

diagnose GERD was not significant in terms of CSA and distensibility, for a total of 40 subjects. Since then, there have been no large-scale studies on the usefulness of EndoFLIP® in the diagnosis of GERD. Therefore, we conducted this study in order to evaluate the usefulness of EndoFLIP® in a large-scale population and to determine the differences between NERD and ERD using EndoFLIP®.

In this study, we have shown that the distensibility index of the ERD, NERD, and control groups were significantly different. The ERD group had the highest distensibility index, while the control group had the smallest. In addition, the ERD group had the highest CSA, while the control group had the lowest. When comparing the results of high-resolution manometry and 24-hour pH monitoring, the integrated relaxation pressure was lower in the ERD group than in the other groups, and 24-hour pH monitoring showed a significant difference in all groups. We demonstrated the usefulness of measuring EGJ distensibility in

diagnosing GERD in a large-scale study of 791 patients. In the diagnosis of GERD through receiver operating characteristic curve analysis, it is important to obtain the distensibility index cutoff value. Furthermore, we have to consider the practical aspects of the EndoFLIP® technique, such as the assessment of the anti-reflux procedure for GERD patients, given that altered distensibility could predict worse symptoms or quality of life after the anti-reflux procedure.[21] In addition, because of expensive cost, EndoFLIP® may be not recommended to all GERD patients. It may be required in some cases, for example, before treatment such as anti-reflux mucosal resection or anti-reflux surgery, or in refractory GERD, as it is thought to be an additive diagnostic method when the information of distensibility is needed.

This study has several limitations. First, we did not investigate the presence of hiatal hernias. Hiatal hernias can alter the pressure when the low esophageal sphincter enters the thorax. It is important to control for the presence of hiatal hernias when measuring the distensibility index among the groups. However, hiatal hernias were difficult to objectify through endoscopic reviews. Second, we divided patients into ERD and NERD groups based on typical reflux symptoms which responded to proton pump inhibitors as in the previous study.[8] By this definition, the NERD group could include reflux hypersensitivity. In this study, the mean values of the DeMeester score of the ERD and NERD groups was less than 14.7 points. We inferred that defining GERD patients based on symptoms might lead to false positive patients, whereas the DeMeester score can lead to highly false negative patients considering that the sensitivity of pH monitoring is 70% to 80%.[12] When diagnosing based on symptoms, some GERD patients showed a low DeMeester score.[11] Therefore, in this study, ERD group was defined according to typical reflux symptoms and endoscopic findings, and NERD was defined according to typical reflux symptoms, endoscopic findings and response

to proton pump inhibitor. Control group was defined according to nonspecific abdominal symptoms, endoscopic findings and pH monitoring. The classification of ERD, NERD, and control group in this study may be confusing. Third, there is a relatively large variability among the patients, and, despite repeating the measurements thrice, the real-time recording may have led to variation during intraprocedural changes. However, since a significant difference was observed between the controls and the patients with GERD, we concluded that EndoFLIP® could provide additional information through the measurement of EGJ function. Fourth, in this study, we only used a 40 mL volume-controlled distension. Although there is no established volume distension during the EndoFLIP® procedure, 30-mL and 40-mL volumes appear to be the most clinically relevant based on previously published data.[22] However, in our study, we standardized the volume to 40 mL and measured the parameters in a 40 mL volume distension, which may serve to reduce the bias among the study groups.

In conclusion, EGJ distensibility in GERD patients showed a significant increase compared to that of the control group, regardless of the presence of erosive esophagitis. In this large-scale study, the measurement of EGJ distensibility using the EndoFLIP® system was helpful in the diagnosis of GERD. In addition to ambulatory pH-impedance tests, high-resolution manometry, and endoscopy, EndoFLIP® is helpful in diagnosing GERD based on objective evidence and in classifying the subtype of GERD.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conceptualization: J.Y.C. Methodology: I.K.Y., E.K. Formal analysis: S.P.H. Writing - original draft: J.M.L. Writing - review and editing: I.K.Y. Approval of final manuscript: all authors.

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