

# Association between endoscopic pressure study integrated system (EPSIS) and high-resolution manometry



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## ABSTRACT

**Background and study aims** The endoscopic pressure study integrated system (EPSIS), a novel diagnostic tool for

gastroesophageal reflux disease (GERD), allows evaluation of the anti-reflux barrier using endoscopy by monitoring the intragastric pressure (IGP) during insufflation. In this study, we evaluated the association between EPSIS results and lower esophageal sphincter (LES) function measured by high-resolution manometry (HRM) to elucidate whether EPSIS can evaluate the LES function.

**Patients and methods** A retrospective, single-center study of patients with GERD symptoms who underwent endoscopy, pH-impedance monitoring, EPSIS, and HRM was conducted. The primary outcome was basal LES pressure and the secondary outcomes were end-respiratory LES pressure and integrated relaxation pressure (IRP). As EPSIS parameters, the following were measured: 1) pressure difference (mmHg), the difference between maximum and basal IGP; and 2) pressure gradient (mmHg/s), calculated by dividing pressure difference by the insufflating time. Pressure difference < 4.7 mmHg or pressure gradient < 0.07 mmHg/s was defined as an EPSIS GERD pattern.

**Results** Forty-seven patients (median age: 53 years, 37 female) were analyzed. Pressure difference and pressure gradient significantly correlated with basal LES pressure ( $\rho = 0.29$ ;  $P = 0.04$  and  $\rho = 0.29$ ;  $P = 0.04$ ). Patients with EPSIS GERD pattern showed significantly lower basal LES pressure [13.2 (4.8–26.6) vs 25.3 (10.4–66.7) mmHg,  $P = 0.002$ ], lower end-respiratory LES pressure [8.5 (1.1–15.9) vs 15.5 (1.9–43.9) mmHg,  $P = 0.019$ ] and lower IRP [5.9 (1.0–12.0) vs 9.8 (1.3–17.8) mmHg,  $P = 0.020$ ].

**Conclusions** This study showed a close association between EPSIS results and LES pressures measured by HRM. This indicates that EPSIS can evaluate the LES function during endoscopy and endorse the role of EPSIS as a diagnostic tool for GERD.

## Introduction

Gastroesophageal reflux disease (GERD) is a common gastrointestinal disorder wherein retrograde flow of gastric contents into the esophagus results in symptoms or complications [1].

The pathophysiological mechanisms involved include transient lower esophageal sphincter relations (TLESRs), low lower esophageal sphincter (LES) pressure, swallow-associated LES relaxations, and straining during periods with low LES pressure [2–5].

The endoscopic pressure study integrated system (EPSIS) is a novel diagnostic tool for GERD. EPSIS allows evaluation of the anti-reflux barrier during endoscopy by monitoring the intra-gastric pressure (IGP) during stomach insufflation [6]. The relation between EPSIS and 24-hour pH-impedance monitoring, the gold standard for diagnosing GERD, has been previously reported by our group [6, 7]. EPSIS showed good accuracy in predicting acid reflux by calculating the maximum IGP and wave form pattern [6]. Subsequently, we found that the EPSIS pressure difference between the maximum IGP and baseline IGP had the best diagnostic accuracy, with an area under the curve of 0.87 [7]. Moreover, a close relationship also was reported between EPSIS and endoscopic findings of erosive esophagitis and Barrett's esophagus (BE) [8].

Although these reports supported the usefulness of EPSIS as a device to evaluate the anti-reflux barrier of the esophagus, the association between EPSIS and high-resolution manometry (HRM) were unknown and it was not determined whether EPSIS can reflect on the LES function as an anti-reflux barrier. Therefore, in this study, we evaluated the association between EPSIS results and the LES function measured by HRM.

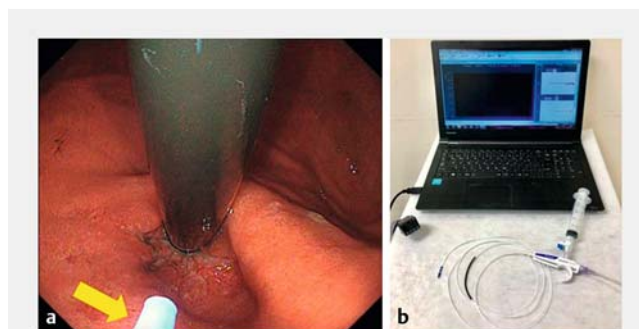
## Patients and methods

This was a retrospective analysis of data collected prospectively at Showa University Koto Toyosu Hospital, Tokyo, Japan, between October 2018 and December 2020. Sixty-two consecutive patients experiencing typical GERD symptoms (heartburn with/without chest pain, belching or regurgitation) who underwent esophagogastroduodenoscopy (EGD), EPSIS, HRM, and 24-hour esophageal pH-impedance monitoring were included. Patients with primary esophageal motility disorders such as achalasia and a history of upper gastrointestinal surgery such as Nissen fundoplication, antireflux mucosectomy (ARMS) [9] or antireflux mucosal ablation (ARMA) [10] were excluded. The primary outcome was basal LES pressure and the secondary outcomes were end-respiratory LES pressure and integrated relaxation pressure (IRP). In our previous report that compared EPSIS results and 24-hour esophageal pH-impedance monitoring [7], some patients underwent HRM to rule out major esophageal motility disorders. A total of 23 patients from the previous report were included in the current study.

## Procedure

### HRM

An HRM system with unisensor catheter (Starlet, Starmedical Inc., Tokyo, Japan) was used. Patients fasted a minimum of 6 hours before the test. Patients were placed in the supine position and the catheter was inserted transnasally after applying lidocaine HCl 2% jelly to the nasal cavity. Catheter position was confirmed using deep inspirations. A baseline period of at least 30 seconds was captured to enable identification of anatomic landmarks including basal LES pressure and end-respiratory LES pressure. Following this, 10 5-mL wet swallows (20–30 seconds between swallows) of water were performed to measure IRP and esophageal peristalsis according to Chicago Classifica-



► **Fig. 1** Endoscopic image of EPSIS procedure. The endoscope is stabilized in the lesser curvature of the stomach in retroflexion, and the through-the-scope catheter of EPSIS is inserted until the tip can be seen. **a** The yellow arrow indicates the tip of the through-the-scope catheter. **b** EPSIS device, through-the-scope catheter, internal pressure measuring device and wave logger software.

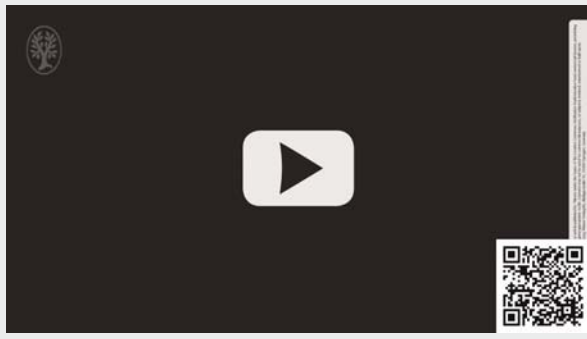
tion v3.0 [11]. Although HRM and EPSIS were performed on the same day, all HRM procedures were carried out before performing EPSIS since EPSIS procedure requires sedation and stomach insufflation.

### EPSIS

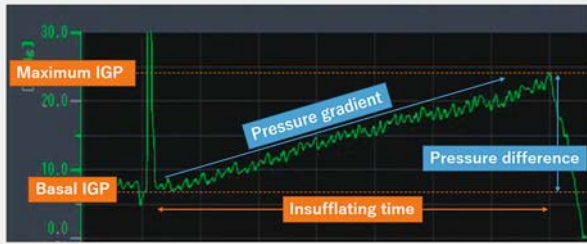
EPSIS procedures were performed after endoscopic assessment of erosive esophagitis and the gastroesophageal junction (GEJ) using high-definition endoscopes (GIF-H260Z/GIF-H290Z; Olympus Corp., Tokyo, Japan). To lessen discomfort caused by the distension of the stomach, all patients were placed in the left lateral position and sedated with intravenous propofol (1%/20 mL). A constant flow volume of approximately 1.5 L/min was achieved using a CO<sub>2</sub> insufflator (UCR; Olympus Corp.) and high flow tube (MAJ-1741; Olympus Corp.). Afterward, insertion of a through-the-scope catheter (PR-V235Q; Olympus Corp.) connected to an internal pressure measuring device (TR-W550, TR-TH08, AP-C35; Keyence, Osaka, Japan) into the stomach through the scope's working channel was carried out (► **Fig. 1b**). Prior to insertion of the catheter, stabilization of the scope in the upper lesser curvature of the stomach approximately 2 cm from the GEJ during retroflexed view was done (► **Fig. 1a**). After confirming the position of the scope, the catheter was advanced through the channel and all excessive CO<sub>2</sub> was suctioned. This is to ensure that there is minimal CO<sub>2</sub> within the stomach prior to insufflating.

Subsequently, continuous insufflation of CO<sub>2</sub> was done until triggering the cardia opening by belching. Wave logger software (NR-500, Keyence) was applied to record IGP and its waveform (► **Video 1**). The waveform was categorized into flat and uphill; the flat waveform was defined as IGP is not built up while insufflating CO<sub>2</sub>, the uphill waveform was defined as IGP is elevated and suddenly released just before the patients' belch. Based on the IGP, following parameters were measured: 1) Basal IGP (mmHg), defined as the IGP at the time of initiating continuous CO<sub>2</sub> insufflation after setting the scope and the catheter; 2) Maximum IGP (mmHg), defined as the IGP at the time of belching with continuous and excessive CO<sub>2</sub> insufflation; 3) In-

## VIDEO



► **Video 1** A video to explain how the endoscopic pressure study integrated system (EPSIS) works.



► **Fig. 2** EPSIS waveform characterization showing the Maximum IGP, Basal IGP and Insufflating time. By these three parameters, pressure gradient and pressure difference were calculated.

sufflating time, the time required to reach maximum IGP from basal IGP (► **Fig. 2**). Based on these parameters, the following were calculated: 1) pressure difference (mmHg), defined as the difference between maximum IGP and basal IGP; 2) pressure gradient of the waveform (mmHg/s), calculated by dividing pressure difference by the insufflating time (► **Fig. 2**). To prevent the formation of a Mallory-Weiss tear, insufflation was discontinued if IGP reached 25 mmHg or at the discretion of the endoscopist after exceeding 20 mmHg. The cut off values of pressure difference and pressure gradient were based on our previous report [7]. Pressure difference of more than 4.7 mmHg and pressure gradient of more than 0.07 mmHg/s were defined as normal on EPSIS, which we named as “EPSIS normal pattern.” Pressure difference of less than 4.7 mmHg or pressure gradient of less than 0.07 mmHg/s were defined as abnormal on EPSIS, which we named as “EPSIS GERD pattern”.

### Endoscopic assessment of GERD and hiatal hernia

Endoscopic assessment of GERD was performed with modified Los Angeles classification system [12, 13]. The assessment of the GEJ including hiatal hernia was performed with CO and SH scale [14]. The assessment was made in retroflex view under excessive and high-flow insufflation until the folds of the greater curvature flattened and when the maximum GEJ opening was observed. Cardiac Opening (CO), the diameter of the opening

of the cardia (cm), and Sliding Hernia (SH), the length from the diaphragmatic crus to the squamocolumnar junction (cm), were measured based on the previous report [14].

### pH-impedance monitoring

Twenty-four-hour esophageal pH-impedance monitoring (ZepHr, Sandhill Scientific, Inc., Colorado, United States) was performed to diagnose acid reflux. Proton-pump inhibitors or vonoprazan was suspended 7 days prior to the examination. Acid exposure time (AET) is defined as percentage of time with pH below 4 at the distal esophagus during 24-hour monitoring, and AET of more than 6% was considered to be definitively abnormal based on the 2018 Lyon Consensus [15].

### Statistical analysis

The median and range were used for continuous variables. Frequency counts and percentage were used for categorical data. We used the Spearman's rank correlation coefficient ( $\rho$ ) to assess the correlation between EPSIS and HRM continuous variables. Differences between “flat waveform”/“uphill waveform” and “EPSIS normal pattern”/“EPSIS GERD pattern” were analyzed using a Chi-squared test or a Fisher's exact test for categorical data, and the Mann-Whitney U test for comparing continuous data. All statistical analyses were conducted using JMP 15.0 (SAS Institute Inc., Cary, North Carolina, United States) and STATA 16.1 (Stata Corp, College Station, Texas, United States).

### Ethical considerations

The study protocol adhered to the principles of the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of Showa University Koto Toyosu Hospital (IRB Registration No: 21T7002). Written informed consent for all procedures were obtained from all participants. In accordance with the IRB, individual informed consent for inclusion in this study was waived. The research outline was appropriately notified on the website of Showa University Koto Toyosu Hospital and an appropriate refusal opportunity was given for the use of medical record information.

## Results

### Study population

A total of 62 patients underwent EGD, EPSIS, HRM and pH-impedance monitoring during the study period. Of them, six patients with a history of prior upper gastrointestinal surgery and nine patients diagnosed with achalasia were excluded. A total of 47 patients with typical GERD symptoms were included in the analysis. Patients' characteristics are summarized in ► **Table 1**.

### EPSIS parameters and high-resolution manometry

First, we explored the correlation between EPSIS parameters (pressure difference and pressure gradient) and LES parameters in HRM (basal LES pressure, end-respiratory pressure and IRP). Pressure difference significantly correlated with basal LES pressure ( $\rho=0.29$ ;  $P=0.04$ ) and end-respiratory LES pressure ( $\rho=$

► **Table 1** Patient characteristics.

Variables	N=47
Age, years, median (range)	53 (18–88)
Female gender	37 (78.7%)
BMI, kg/m <sup>2</sup> , median (range)	21.2 (14.6–33.3)
Endoscopic findings	
GERD (Modified Los Angeles Classification)	
▪ Grade N	0 (0%)
▪ Grade M	38 (80.9%)
▪ Grade A	5 (10.6%)
▪ Grade B	4 (8.5%)
▪ Grade C	0 (0%)
▪ Grade D	0 (0%)
Cardiac opening, cm, median (range)	2 (1–5)
Sliding hernia, cm, median (range)	1 (0–3)
24 hours pH monitoring findings	
▪ AET, %, median (range)	2.8 (0–67.3)
▪ AET >6%	16 (33.0%)
EPSIS findings	
▪ Uphill waveform	32 (68.1%)
▪ Flat waveform	15 (31.9%)
Pressure difference >4.7, mmHg	37 (78.7%)
Pressure gradient >0.07, mmHg/s	39 (83.0%)
EPSIS pattern	
▪ EPSIS Normal pattern	37 (78.7%)
▪ EPSIS GERD pattern	10 (21.3%)
HRM findings	
▪ Basal LES pressure, mmHg, median (range)	21.2 (4.8–66.7)
▪ End-respiratory LES pressure, mmHg, median (range)	13.8 (1.1–43.9)
▪ IRP, mmHg, median (range)	9.2 (1.0–17.8)
EPSIS normal pattern is defined as pressure difference >4.7 and pressure gradient >0.07. BMI, body mass index; AET, acid exposure time; EPSIS, endoscopic pressure study integrated system; GERD, gastroesophageal reflux disease; HRM, high-resolution manometry; LES, lower esophageal sphincter; IRP, integrated relaxation pressure	

0.29;  $P=0.04$ ), while pressure gradient significantly correlated with basal LES pressure ( $I=0.29$ ;  $P=0.04$ ). EPSIS parameters did not correlate with IRP (► **Table 2**).

### “Uphill waveform” and “flat waveform”

Additionally, we tested whether EPSIS “Uphill waveform” and “Flat waveform” were associated with LES pressures. Thirty-two patients (68.1%) showed uphill waveform and 15 patients

(31.9%) showed flat waveform. Patients with flat waveform showed significantly lower basal LES pressure [14.6 (4.8–33.5) vs 25.0 (10.4–66.7) mmHg,  $P=0.019$ ] and lower end-respiratory LES pressure [9.2 (1.1–19.1) vs 15.5 (1.9–43.9) mmHg,  $P=0.023$ ]. Likewise, patients with flat waveform had a significantly larger cardiac opening [3 (1–5) vs 1 (1–3) cm,  $P=0.002$ ] and larger sliding hernia [2 (1–3) vs 1 (0–3) cm,  $P=0.001$ ], [median (range)] (► **Table 3**).

### “EPSIS normal pattern” and “EPSIS GERD pattern”

Lastly, we tested whether “EPSIS normal pattern” and “EPSIS GERD pattern” were associated with LES pressures. Thirty-seven patients (78.7%) were diagnosed with EPSIS normal pattern and 10 patients (21.3%) were diagnosed with EPSIS GERD pattern. Compared to patients with EPSIS normal pattern, patients with EPSIS GERD pattern had significantly lower basal LES pressure [13.2 (4.8–26.6) vs 25.3 (10.4–66.7) mmHg,  $P=0.002$ ], lower end-respiratory LES pressure [8.5 (1.1–15.9) vs 15.5 (1.9–43.9) mmHg,  $P=0.019$ ], and lower IRP [5.9 (1.0–12.0) vs 9.8 (1.3–17.8) mmHg,  $P=0.020$ ], [median (range)] (► **Table 4**).

## Discussion

In this study, we assessed the link between EPSIS (which evaluates the anti-reflux barrier during endoscopy) and the LES function measured by HRM. Our results showed that EPSIS parameters correlated with LES pressures and endorse the role of EPSIS as a diagnostic tool for GERD from a pathophysiological perspective. Patients with flat waveform and EPSIS GERD pattern showed significantly lower basal and end-respiratory LES pressures.

EPSIS is a novel device to measure the IGP until triggering the cardia opening by belching during air insufflation. Previously, we reported that EPSIS findings correlated well with acid reflux measured by 24-hour pH-impedance monitoring [6]. In another study, we reported a close relationship between EPSIS findings and endoscopic erosive esophagitis and BE [8]. These results indicated the clinical ability of EPSIS to evaluate the anti-reflux barrier of the esophagus. Here, we found a significant relationship between EPSIS results and LES pressure in HRM, which suggests that the anti-reflux barrier assessed by EPSIS can indirectly estimate the LES function. Based on the available literature, patients with pathological acid reflux had significantly lower basal LES pressure and lower IRP [16]. Previous reports have also shown that patients with hiatal hernia [17] and GERD symptoms [18] had lower basal LES pressure. These facts show that the anti-reflux function of the esophagus can be partially evaluated by LES pressures. In addition, basal and end-respiratory LES pressure and IRP are reproducible and standardized parameters during HRM [11, 19], which is why we selected these parameters in this study.

By exploring the correlation between EPSIS parameters and LES parameters in HRM, we found that EPSIS pressure difference (Maximum IGP – Basal IGP) showed the closest correlation with basal and end-respiratory LES pressure, coinciding with our report that identified pressure difference as the most reliable parameter to predict abnormal acid reflux [7]. Interesting-

► **Table 2** EPSIS findings and LES contractility measured by high-resolution manometry.

	Basal LES pressure	End-respiratory LES pressure	IRP
EPSIS pressure difference	<b><math>\rho = 0.29</math>; <math>P = 0.04</math></b>	<b><math>\rho = 0.29</math>; <math>P = 0.04</math></b>	$\rho = 0.17$ ; $P = 0.24$
EPSIS pressure gradient	<b><math>\rho = 0.29</math>; <math>P = 0.04</math></b>	$\rho = 0.21$ ; $P = 0.15$	$\rho = 0.12$ ; $P = 0.4$

EPSIS, endoscopic pressure study integrated system; LES, lower esophageal sphincter; IRP, integrated relaxation pressure;  $\rho$ , Spearman's rank correlation coefficient. Figures in bold denote statistical significance.

► **Table 3** Association between EPSIS waveform (flat/uphill) and patient characteristics including high-resolution manometry.

	Flat waveform N = 15	Uphill waveform N = 32	P value
Age, years, median (range)	53 (25–78)	54 (18–88)	0.95
Sex female (%)	9 (60.0)	28 (87.5)	0.054
BMI, kg/m <sup>2</sup> , median (range)	24.8 (17.5–33.3)	20.0 (14.6–29.0)	<b>0.005</b>
GERD LA Classification (Grade N/M/A/B/C/D) (%)	0/10/2/3/0/0 (0/66.7/13.3/20/0/0)	0/28/3/1/0/0 (0/87.5/9.4/3.1/0/0)	0.10
Erosive esophagitis (Grade A-D) (%)	5 (33.3)	4 (12.5)	0.12
Cardiac opening, cm, median (range)	3 (1–5)	2 (1–3)	<b>0.002</b>
Sliding hernia, cm, median (range)	2 (1–3)	1 (0–3)	<b>0.002</b>
AET, %, median (range)	26 (1.5–65.3)	1.3 (0–67.3)	<b>&lt;0.001</b>
AET > 6% (%)	11 (73.3)	5 (15.6)	<b>&lt;0.001</b>
Basal LES pressure, mmHg, median (range)	14.6 (4.8–33.5)	25.0 (10.4–66.7)	<b>0.019</b>
end-respiratory LES pressure, mmHg, median (range)	9.2 (1.1–19.1)	15.5 (1.9–43.9)	<b>0.023</b>
IRP, mmHg, median (range)	7.6 (1.0–15.1)	9.9 (1.3–17.8)	0.096

EPSIS, endoscopic pressure study integrated system; BMI, body mass index; LA Classification, Los Angeles Classification; AET, acid exposure time; LES, lower esophageal sphincter; IRP integrated relaxation pressure. Figures in bold denote statistical significance.

ly, the association between EPSIS parameters and the IRP was weaker, possibly because the IRP provides information on the degree of GEJ relaxation during swallowing, rather than a parameter that reflects the basal LES competence [19].

When dividing the patients into EPSIS “flat waveform” and “uphill waveform”, patients with flat waveform showed significantly lower LES pressures. Similarly, when patients were divided into “EPSIS GERD pattern” and “EPSIS Normal pattern”, patients with EPSIS GERD pattern showed significantly lower LES pressures. Both the flat waveform and EPSIS GERD pattern respectively reflect the inability of the LES to retain the CO<sub>2</sub> in the stomach, thus showing lower LES pressures. However, the decision of flat/uphill waveform could be sometimes subjective, therefore we characterized the waveform objectively using pressure gradient and pressure difference to describe the EPSIS results quantitatively [7]. Accordingly, we think that EPSIS GERD/Normal pattern is more suitable to describe EPSIS results than flat/uphill waveform in order to find true GERD patients out of GERD suspected patients in clinical settings.

Furthermore, EPSIS parameters showed a tendency to correlate with the size of cardiac opening and sliding hernia as endoscopic findings. The cardiac opening, which describes the size

of esophageal hiatus made by diaphragmatic crura, and the degree of sliding hernia are the key anatomical changes of the anti-reflux barrier in GERD patients [14]. Considering that the previous reports showed that the size of cardiac opening and sliding hernia are correlated with acid reflux [14], and the results of the current study showed that the size of cardiac opening and sliding hernia correlate with EPSIS results, CO and SH scale [14] may be useful in predicting the LES function in GERD patients when only using endoscopy.

On a separate note, TLESR is the most important mechanism of GERD, and most of the acid reflux occur during TLESR [3–5]. TLESR, a mechanism of belching, is triggered by gastric distension caused by gas or meals [5, 20, 21]. EPSIS is a device to measure the IGP in triggering the cardia opening by belching during air insufflation. Therefore, we hypothesize that maximum IGP is thought to coincide with the threshold of IGP to cause TLESR by air insufflation, and could explain why the ability of EPSIS to predict acid reflux (AUC > 0.80) [7], which is defined by 24-hour pH-impedance monitoring, is beyond its correlation with LES pressure. However, in this study, we did not analyze TLESR. These can be detected by HRM, but most occur after meals and are, therefore, not detected by parameters ac-

► **Table 4** Association between “EPSIS GERD pattern”/“EPSIS Normal pattern” and patient characteristics including high-resolution manometry.

	<b>EPSIS GERD pattern N = 10</b>	<b>EPSIS Normal pattern N = 37</b>	<b>P value</b>
Age, years, median (range)	53 (30–75)	52 (18–88)	0.77
Sex female (%)	8 (80)	29 (78.4)	1.00
BMI, kg/m <sup>2</sup> , median (range)	23.0 (17.7–33.3)	21.0 (14.6–29.0)	0.19
GERD LA Classification (Grade N/M/A/B/C/D) (%)	0/7/1/2/0/0 (0/70.0/20.0/10.0/0/0)	0/31/4/2/0/0 (0/83.8/10.8/5.4/0/0)	0.24
Erosive esophagitis (Grade A-D) (%)	3 (30)	6 (16.2)	0.38
Cardiac opening, cm, median (range)	2 (1–5)	2 (1–4)	0.056
Sliding hernia, cm, median (range)	1.5 (1–3)	1 (0–3)	0.13
AET, %, median (range)	20.2 (0.7–65.3)	1.5 (0–67.3)	<b>0.010</b>
AET > 6 % (%)	7 (70.0)	9 (24.3)	<b>0.020</b>
Basal LES pressure, mmHg, median (range)	13.2 (4.8–26.6)	25.3 (10.4–66.7)	<b>0.002</b>
end-respiratory LES pressure, mmHg, median (range)	8.5 (1.1–15.9)	15.5 (1.9–43.9)	<b>0.019</b>
IRP, mmHg, median (range)	5.9 (1.0–12.0)	9.8 (1.3–17.8)	<b>0.020</b>

EPSIS, endoscopic pressure study integrated system; BMI, body mass index; LA Classification, Los Angeles Classification; AET, acid exposure time; LES, lower esophageal sphincter; IRP integrated relaxation pressure.  
Figures in bold denote statistical significance.

quired during standard HRM protocol with water swallows [11], which is the protocol that was used in this study.

In addition, we speculate that the reason why the correlation coefficient between EPSIS parameters and LES parameters in this study was weak ( $\rho = 0.29$ ;  $P = 0.04$ ) might be because we did not analyze TLESR. TLESR is mainly related to mild GERD, and low LES pressure is mainly related to severe GERD with free reflux [2]; however, the cohort in this study were mostly comprised of mild GERD patients. Further studies to investigate the correlation between TLESR and EPSIS results are expected.

Previously, manometry was necessary to evaluate the LES pressure, requiring an additional lengthy and invasive procedure. However, EPSIS is an easy device which can be performed during screening endoscopy within a few minutes. By using EPSIS, LES pressure can be easily predicted and this will be beneficial to diagnose GERD, including those without endoscopic erosive esophagitis.

Certain limitations should be recognized in this study. Sedation with propofol is used to reduce patient distress due to gastric dilatation when performing EPSIS. Although previous data suggest that propofol does not have a great impact on LES pressure [22], the sedation may affect the lower and upper esophageal sphincter contraction. In addition, the depth of the sedation may also affect the threshold of causing belching affecting the result of IGP. HRM, on the other hand, is performed without sedation. Another limitation is that the basal LES pressure in HRM is measured during resting, whereas maximum IGP in EPSIS is the maximum pressure during insufflation. In other words, EPSIS is a kind of “air sufflation tolerance test” to measure the anti-reflux barrier. In future studies, measuring the LES pressure by HRM just before TLESR occurs by insufflating air

into the stomach and comparing it with the IGP in EPSIS are expected. Finally, this is a retrospective study with limited sample size. Due to the retrospective nature, we did not have data regarding detailed GERD symptoms or medication history which may affect LES pressure such as Ca-blockers or nitrates. Larger and more detailed studies, which may include healthy volunteers, are needed to clarify the relationship between EPSIS results and HRM, including newly proposed GEJ functional parameters such as the GEJ contractile integral [23, 24].

## Conclusions

In summary, this study found a close relationship between EPSIS and LES pressures measured by HRM. Patients with flat waveform and EPSIS GERD pattern showed significantly lower basal LES pressure. These results indicate that EPSIS can evaluate the LES function during endoscopy and endorse the role of EPSIS as a diagnostic tool for GERD from a pathophysiological perspective.

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## Competing interests

Dr. Inoue is an advisor of Olympus Corporation and Top Corporation. He has also received educational grants from Olympus Corp., and Takeda Pharmaceutical Co.

## References

- [1] Vakil N, van Zanten SV, Kahrilas P et al. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol* 2006; 101: 1900–1920 quiz 1943
- [2] Tack J, Pandolfino JE. Pathophysiology of gastroesophageal reflux disease. *Gastroenterology* 2018; 154: 277–288
- [3] Schoeman MN, Tippet MD, Akkermans LM et al. Mechanisms of gastroesophageal reflux in ambulant healthy human subjects. *Gastroenterology* 1995; 108: 83–91
- [4] Iwakiri K, Kawami N, Sano H et al. Mechanisms of excessive esophageal acid exposure in patients with reflux esophagitis. *Dig Dis Sci* 2009; 54: 1686–1692
- [5] Dodds WJ, Dent J, Hogan WJ et al. Mechanisms of gastroesophageal reflux in patients with reflux esophagitis. *N Engl J Med* 1982; 307: 1547–1552
- [6] Inoue H, Shimamura Y, Rodriguez de Santiago E et al. Diagnostic performance of the endoscopic pressure study integrated system (EPSIS): a novel diagnostic tool for gastroesophageal reflux disease. *Endoscopy* 2019; 51: 759–762
- [7] Shimamura Y, Inoue H, de Santiago ER et al. Characterization of intragastric pressure waveform in Endoscopic Pressure Study Integrated System: a novel diagnostic device for gastroesophageal reflux disease. *Dig Endosc* 2021; 33: 780–787
- [8] Iwaya Y, Inoue H, Rodríguez de Santiago E et al. Endoscopic pressure study integrated system reflects gastroesophageal junction competence in patients with erosive esophagitis and Barrett’s esophagus. *Dig Endosc* 2020; 32: 1050–1056
- [9] Inoue H, Ito H, Ikeda H et al. Anti-reflux mucosectomy for gastroesophageal reflux disease in the absence of hiatus hernia: a pilot study. *Ann Gastroenterol* 2014; 27: 346–351
- [10] Inoue H, Tanabe M, de Santiago ER et al. Anti-reflux mucosal ablation (ARMA) as a new treatment for gastroesophageal reflux refractory to proton pump inhibitors: a pilot study. *Endosc Int Open* 2020; 8: E133–E138
- [11] Kahrilas PJ, Bredenoord AJ, Fox M et al. The Chicago Classification of esophageal motility disorders, v3.0. *Neurogastroenterol Motil* 2015; 27: 160–174
- [12] Hongo M. Minimal changes in reflux esophagitis: red ones and white ones. *J Gastroenterol* 2006; 41: 95–99
- [13] Hoshihara Y, Hashimoto M. Endoscopic classification of reflux esophagitis. *Nihon Rinsho* 2000; 58: 1808–1812
- [14] Inoue H, Fujiyoshi Y, Abad MRA et al. A novel endoscopic assessment of the gastroesophageal junction for the prediction of gastroesophageal reflux disease: a pilot study. *Endosc Int Open* 2019; 7: E1468–E1473
- [15] Gyawali CP, Kahrilas PJ, Savarino E et al. Modern diagnosis of GERD: the Lyon Consensus. *Gut* 2018; 67: 1351–1362
- [16] Jain M, Srinivas M, Bawane P et al. Basal lower esophageal sphincter pressure in gastroesophageal reflux disease: An ignored metric in high-resolution esophageal manometry. *Indian J Gastroenterol* 2018; 37: 446–451
- [17] Sloan S, Rademaker AW, Kahrilas PJ. Determinants of gastroesophageal junction incompetence: hiatal hernia, lower esophageal sphincter, or both? *Ann Intern Med* 1992; 117: 977–982
- [18] Ahtaridis G, Snape WJ Jr., Cohen S. Lower esophageal sphincter pressure as an index of gastroesophageal acid reflux. *Dig Dis Sci* 1981; 26: 993–998
- [19] Trudgill NJ, Sifrim D, Sweis R et al. British Society of Gastroenterology guidelines for oesophageal manometry and oesophageal reflux monitoring. *Gut* 2019; 68: 1731–1750
- [20] Wyman JB, Dent J, Heddl R et al. Control of belching by the lower oesophageal sphincter. *Gut* 1990; 31: 639–646
- [21] Holloway RH, Kocyan P, Dent J. Provocation of transient lower esophageal sphincter relaxations by meals in patients with symptomatic gastroesophageal reflux. *Dig Dis Sci* 1991; 36: 1034–1039
- [22] de Leon A, Ahlstrand R, Thörn SE et al. Effects of propofol on oesophageal sphincters: a study on young and elderly volunteers using high-resolution solid-state manometry. *Eur J Anaesthesiol* 2011; 28: 273–278
- [23] Nicodème F, Pipa-Muniz M, Khanna K et al. Quantifying esophago-gastric junction contractility with a novel HRM topographic metric, the EGJ-Contractile Integral: normative values and preliminary evaluation in PPI non-responders. *Neurogastroenterol Motil* 2014; 26: 353–360
- [24] Tolone S, De Bortoli N, Marabotto E et al. Esophagogastric junction contractility for clinical assessment in patients with GERD: a real added value? *Neurogastroenterol Motil* 2015; 27: 1423–1431