Title: Esophagogastric Junction Morphology and Distal Esophageal Acid Exposure

Short running head: EGJ morphology and esophageal reflux

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Abstract

Background

The Chicago classification has recently added a morphological sub-classification for the esophagogastric junction (EGJ). Our aim was to assess the distal esophageal acid exposure in patients with this new Chicago EGJ- type IIIa and IIIb classification.

Study Design

From a prospectively collected high resolution manometry (HRM) database, we identified patients who underwent 24-hour pH study between October 2011-June 2015 and were diagnosed with EGJ-type III based on HRM. Chicago EGJ-type III is defined as the inter-peak nadir pressure≤gastric pressure and a lower esophageal sphincter (LES)–crural diaphragm (CD) separation >2cm [IIIa-pressure inversion point (PIP) remains at CD level, IIIb-PIP remains at LES level]. We classified the patients into reflux group [DeMeester score >14.72 or Fraction time pH (<4) >4.2%] and non-reflux group based on 24-hour pH study.

Results

Fifty patients were identified that satisfied the study criteria, of which 37 patients (74%) were EGJ-type IIIa. In those with EGJ-type IIIb, abdominal LES length (AL) in reflux group was significantly shorter than the non-reflux group (0.8 vs. 1.8, p<0.05). EGJ-type IIIa patients showed significantly higher value for DeMeester score and Fraction time pH, and more often had a positive pH study than EGJ-type IIIb patients (DeMeester score: 26.7 vs. 11.7, p<0.05; Fraction time pH: 7.9 vs.2.6, p<0.05; positive pH study: 81.1% vs. 30.8%, p<0.001). Reflux was more common in LES-CD ≥3cm than those with LES-CD <3cm (85% vs. 56.7%, p<0.05).

Conclusion

A subset of patients with >2 cm LES-CD separation (type IIIb) maintain a physiological intra-abdominal location of the EGJ and hence are less likely to have reflux. A LES-CD≥3cm seems to discern a hiatus hernia of clinical significance.

Keywords

Crural diaphragm; gastroesophageal reflux disease; hiatal hernia; high resolution manometry; lower esophageal sphincter; pressure inversion point

Abbreviations: EGJ, esophagogastric junction; LES, lower esophageal sphincter; CD, crural diaphragm; PIP, pressure inversion point; HRM, high resolution manometry; OL, overall LES length; AL, abdominal LES length; LESP, LES pressure; LESPI, LESP integral; IRP, integrated relaxation pressure; DCI, distal contractile integral; GERD, gastroesophageal reflux disease.

Introduction

The esophagogastric junction (EGJ) is the physiological barrier which prevents retrograde reflux of gastric contents into the low-pressure esophagus. It is comprised of an intrinsic high-pressure zone [the lower esophageal sphincter (LES)] within the visceral wall and the crural diaphragm (CD). Functional competence of EGJ in part relies on the intra-abdominal location of the LES. The phreno-esophageal ligament anchors the high pressure zone /LES to the CD. The pressure inversion point (PIP), or respiratory inversion point, is defined as the location at which the inspiratory EGJ pressure becomes less than the expiratory EGJ pressure [1][2]. The PIP is considered to be the physiological boundary between thoracic and abdominal cavity, while the CD is the anatomical one. In patients with a hiatal hernia, abdominal viscera (the stomach) protrudes into the thoracic cavity through the hiatus, [3] disrupting the normal relationship of the EGJ components and potentially adversely affecting its barrier function.

High resolution manometry (HRM) allows for assessment of esophageal function based on the topographical representation of intra-luminal pressure changes. Manometric parameters of EGJ competence were first elucidated by Zanninoto et al [4] using a conventional water perfused system. They showed that in addition to total LES length (TL) and LES pressure (LESP), the length of abdominal component of the LES (AL) was critical for maintaining competence of the EGJ barrier function. These were further confirmed using HRM by Hoshino et al [5]. The abdominal length of the LES is of paramount importance in order to maintain its functional integrity; however, there is still a subset of hiatal hernia patients who do not have reflux.

Recent report suggests that a LES-CD separation of over >1.85cm is associated with an endoscopic/radiographic hiatal hernia [6]. In 2015, the Chicago classification 3.0 was introduced to include a EGJ morphology and LES-CD separation of >2 cm (defined as hiatal hernia) was classified as a Chicago type III [7][8]. Our aim in this study was to assess EGJ morphology of Chicago EGJ-type III subtypes on HRM and their association with distal esophageal acid exposure.

Materials and Methods

Subjects

All patients undergoing esophageal function testing at Creighton University Medical Center are entered in a prospectively maintained database. After Institutional Review Board approval, the database was queried to identify patients who underwent 24-hour pH monitoring and HRM within 1-week interval between October 2011 and June 2015. The studies were reassessed and the EGJ reclassified based on Chicago 3.0 classification [8]. We excluded patients with prior foregut intervention, pH study done on acid suppression medications (proton pump inhibitors ≤7 days or H2 receptor antagonists ≤3 days before 24-hour pH monitoring), esophageal dysmotility or LES-CD >5cm (large hiatal hernia). Patients found to have EGJ-type III configuration on HRM were identified and formed the cohort of the study. We classified the patients into a reflux group [DeMeester score >14.72 or Fraction time pH (<4) >4.2%] or a non-reflux group on 24-hour pH monitoring. Majority of patients were referred for testing as part of work-up for potential surgical intervention.

High Resolution Manometry

HRM was performed with a 36-channel probe with circumferential sensors at 1 cm intervals (Sierra Scientific Instruments Inc., Los Angeles, CA, USA). All manometric studies were re-analyzed and reviewed using Manoview software (Sierra Scientific Instruments Inc.) by a single author (SA) who was blinded to the outcome of the pH study. The pressure topography of ten wet swallows were analyzed using the Chicago classification 3.0 [8]. Esophageal dysmotility was defined as achalasia, EGJ outflow obstruction, major disorders of peristalsis (absent contractility, distal esophageal spasm and hyper-contractile esophagus) or minor disorders of peristalsis (ineffective esophageal motility or fragmented peristalsis). We assessed the overall

LES length (OL), abdominal LES length (AL), LES pressure (LESP), LESP integral (LESPI), integrated relaxation pressure (IRP) and distal contractile integral (DCI) (Figure 1). LESPI is calculated by enclosing the domain of the LES area during a 10 second period using a DCI tool with 20 mmHg isobaric contour at rest without swallows [5]. This measurement has also been included in subsequent studies by others but rechristened as the EGJ contractile integral (EGJ-CI) [9]. PIP is the axial position along the EGJ at which the inspiratory pressure became less than the expiratory pressure [1][2] and marks the physiological transition from the peritoneal cavity to the thoracic cavity. The Chicago classification is defined as: type I-complete overlap of the CD and LES components, type II-the inter-peak nadir pressure > gastric pressure and LES-CD separation of 1-2cm, type III-the inter-peak nadir pressure ≤ gastric pressure [IIIa-PIP remains at the CD level, IIIb-PIP remains at the LES level] (Figure 2).

Hour pH monitoring

Twenty-four-hour pH monitoring was performed using either a catheter-based system (Digitrapper 400pH®; Medtronic, Minneapolis, MN) or a capsule-based system (Bravo®; Medtronic, Minneapolis, MN). The catheter based pH probe was passed transnasally and positioned 5cm above the upper border of the manometrically defined LES, while the capsule was passed transorally and positioned 6 cm above the endoscopic gastroesophageal junction. For the capsule based system, the pH<4 Fraction time and the DeMeester score were the mean of the scores over 2 days. A positive pH study was one where the total time pH< 4 for > 4.2% of the study time.

Statistical analysis

Characteristics of the HRM and 24-hour pH monitoring were summarized using the median values and interquartile range. Independent-sample t-test or Mann–Whitney U-test were used to compare group means in univariable analysis. Medians for skewed data were compared using the Mann–Whitney U-test. Bootstrapping was used to achieve normal distribution. Categorical variables were reported as number and proportion (%) and Pearson's $\chi2$ (chi-square) test was used to compare groups in univariable analysis. The Fisher exact test was used when the numerator was 5 or less or when comparing the rate of a positive pH study. Statistical significance was set at $p<0.05$. SPSS® version 22 was used for all statistical analysis.

Results

Four hundred and seven patients underwent 24-hour pH monitoring and HRM during the study period. Of these, 357 patients were excluded [prior foregut intervention (n=50), on antireflux medications (n=29), esophageal dysmotility (n=108), LES-CD >5cm (n=8) and Chicago type I or II (n=162)], leaving 50 patients who satisfied the cohort of this study. The mean age was 53 years with 14 (28%) male patients.

Assessment of HRM values

Of the 50 patients, 34 patients (68 %) had pathological reflux. The manometric values are shown in Table 1. The AL in the reflux patients [median- 0 cm (range 0-0.6)] was significantly shorter than the AL in the non-reflux group [median- 1 cm (range 0-1.8)]. OL, LESP, LESPI, IRP and DCI were not significantly different between the two groups. The AL, LESP and LESPI were significantly higher in the EGJ-type IIIb group as compared to the EGJ-type IIIa group (Table 2). Individual HRM factors in both the EGJ-type IIIa and the EGJ-type IIIb groups were compared between the reflux and the non-reflux groups. Among the EGJ-type IIIb patients, AL in the reflux group (0.8 cm) was significantly shorter than the AL in the non-reflux group (1.8 cm) (Table 3). The other parameters did not have significant differences.

Assessment of the length of LES-CD

The proportion of patients with reflux was significantly more common in patients with a LES-CD ≥3 cm than in patients with a LES-CD <3cm (85% vs. 56.7%, p=0.046) (Figure 3). The LES-CD length of <3cm was predictive of a negative pH study with a sensitivity of 81.3%, specificity of 50%, positive predictive value of 43.3%, and negative predictive value of 85%. There was no significant difference in the proportion of patients with reflux between LES-CD ≥2.5cm and LES-CD <2.5cm (75% vs. 40%, p=0.423); however, reflux in the LES-CD ≥3.5cm group was significantly more common than in the LES-CD <3.5cm group (100% vs. 61%, p=0.027).

Assessment of the EGJ-types

The DeMeester score, Fraction time pH (<4) and rate of a positive pH study were significantly higher in the EGJ-type IIIa group than in the EGJ-type IIIb group (Table 2). The presence of a EGJ-type IIIb complex had a sensitivity of 56.3%, specificity of 88.2%, positive predictive value of 69.2%, and negative predictive value of 81.1% in diagnosing a negative pH study. When we categorized the patients with a EGJ-type IIIa complex and a EGJ-type IIIb complex using a 3cm LES-CD length as a cut-off, the subgroup of patients with a EGJ-type IIIb complex and a LES-CD <3cm showed the lowest propensity for a positive pH study, while the subgroup with a EGJ-type IIIa complex and a LES-CD ≥3cm showed the highest rate of positive pH study [LES-CD <3cm; EGJ-type IIIa 73.7% (14/19) vs. EGJ-type IIIb 27.3% (3/11); LES-CD ≥3cm; EGJ-type IIIa 88.9% (16/18) vs. EGJ-type IIIb 50% (1/2)].

Discussion

Gastroesophageal reflux disease (GERD) is a common disease with prevalence of approximately 20% in the US population [10]. A hiatal hernia has been shown to be associated with reflux [11][12] and is most readily identified on endoscopic/ radiographic assessment. GERD patients with a hiatal hernia have a greater Fraction time pH<4 score and a higher incidence of reflux episodes [13]. GERD patients with a hiatal hernia have a higher requirement of proton pump inhibitors than GERD patients without a hiatal hernia [14]; however, a subset of hiatal hernia patients do not have symptomatic reflux.

A competent EGJ barrier prevents backflow of gastric contents from the high pressure intra-abdominal stomach to the low pressure intra-thoracic esophagus. In the native (non-diseased) state, the distal esophagus lies in the abdomen. The physiological benefit of this is that the increases in intra-abdominal pressure, which tend to promote backflow of gastric contents, simultaneously reinforces the LES. This is diagrammatically represented in Fig 4a. One can envision that in patients without a hiatal hernia (Fig 4a), an increase in the intra-abdominal pressure works as an ‘external reinforcement’ of the EGJ to counteract similar increases in the intraluminal gastric pressure. However, patients with a hiatal hernia appear to be without this advantage as their LES is intra-thoracic (Fig 4b). In such a situation, increases in the intra-abdominal pressure (bending, lifting etc.) would promote a backflow of gastric contents (Fig 4b).

In the era of conventional water perfused manometry, a hiatal hernia was discerned with notation of a double hump configuration [4]. HRM has revolutionized data acquisition and interpretation of pressure changes within the esophageal lumen. Initially, the assessment of the LES complex with HRM was limited to measurement of the IRP (or eSleeve 3-s nadir) [15][16]. Subsequently, greater focus has shifted to the EGJ, which consists of the diaphragmatic crus (CD) and the intrinsic sphincter (LES). In subjects without a hiatal hernia, the CD and LES have complete overlap, while a double high pressure configuration is associated with LES-CD separation. Patients with a larger separation are associated with a bigger hiatal hernia [17]. The Chicago 3.0 classification proposed a morphological sub-classification based on the LES-CD separation and PIP location. There were three subcategories (type I-III) based on the LES–CD separation with type-III (LES-CD >2cm) further sub-classified into IIIa and IIIb dependent on the PIP position [7][8]. Subsequently, Weijenborg et al reported that HRM has greater sensitivity and specificity for a hiatal hernia than endoscopy and barium swallow. They further noted that a LES-CD ≥1.85cm was associated with a hiatal hernia identifiable with endoscopy and/or radiography [6]. As an index to the functional strength of the LES, Hoshino et al proposed LESPI (measured using DCI tool with 20 mmHg isobaric contour and for a 10 sec duration) as a surrogate of LES pressure and length in the resting state. They showed that a low LESPI was associated with increased reflux [5]. Subsequently Kahrilas et al [8] modified the measurement of this parameter by setting the isobaric contour pressure 2mmHg above gastric pressure and measuring over 3 respiratory cycles- they termed this EGJ-CI (esophagogastric junction – Contractile Integral) and incorporated it in Chicago v3.0 classification. Unfortunately, none of these studies have taken into account the basic functional necessity of the LES-CD overlap (i.e. creating an effective high pressure barrier to reflux of gastric contents). One can safely argue that a small hernia is of no clinical relevance unless it contributes to a pathological dysfunction of the LES-complex (i.e. allowing reflux). Others have also correlated the LES-CD separation with reflux, and with a greater separation being associated with more reflux episodes [18]. This present study adds to the understanding that within the >2 cm LES-CD separation group, there is a subgroup of patients who do not have reflux and can be identified by relative position of PIP to LES. The study proposes a physiological basis as to why this happens.

Our study shows that patients with a type IIIb LES complex are significantly less likely to have reflux compared to those with a type IIIa complex (31% vs 81%). The majority of patients with a type IIIb physiology do not have reflux in spite of a hiatus hernia. This implies that these patients still maintain competence of the EGJ. It is interesting to note that the LESPI measurement of pressure over time in a resting state was low in both groups (compared to patients without a hiatal hernia–data not shown) and did not differ significantly. The reason for a low LESPI is that the spatial separation of the LES and CD lowers the pressure measurement of the LES: this happens in both type IIIa and type IIIb patients. Therefore, one would expect that a low LESPI in both groups would "allow a similar amount" of reflux, but in reality, the type IIIa patients have significantly more reflux than those with a type IIIb complex. The reason of this possible "external reinforcement" of EGJ in a dynamic state is due to the intra-abdominal pressure transmitted through the hernia sac (EGJ type IIIb). Figure 5 is a proposed mechanism by which type IIIb patients continue to enjoy the external re-enforcement compared to type IIIa.

We have specifically made the decision not to include patient reported symptoms as in our experience, symptoms do not correlate with objective testing consistently. The main purpose of this study was to identify subgroups of patients within Type III EGJ morphology who are more likely to have objective pathological reflux and whether they can be identified based on HRM parameters.

This study has limitations, foremost, being that it is a retrospective analysis of data; however, all data was collected prospectively and analyzed in a blind fashion. Perhaps a greater limitation is using a DeMeester score >14.72 or Fraction time pH (<4) >4.2% as a hard cut-off for the presence or absence of GERD. It would have been better to measure the degradation of the LES competence against a progressively rising reflux. However, at present, the 24-hour pH is the gold standard for pathological reflux. Additionally, the sample size of the type IIIb patients with/without reflux was small, introducing the possibility of a type II error. Another drawback of using only distal esophageal acid exposure as a measurement of the degree of reflux, is that it has been shown that even in patients not on acid suppression, up to 10-15% of reflux episodes may be of a pH>4 and hence not assessed using a pH study [19]. Given that there should be no difference in the percentage of reflux episodes missed [pH >4] between the groups, this should not affect the overall conclusions. Another potential limitation could be that majority of the patients were referred for the esophageal testing to the senior author (SKM- a surgeon) for potential surgical intervention and hence may not represent the general patient population with GERD.

In conclusion, we have shown that a subset of patients with a hiatal hernia (morphological type III LES-complex) maintain a physiological intra-abdominal location (type IIIb–PIP above LES) and are less likely to have reflux than those where the LES is abnormally displaced into the physiological intra-thoracic location (type IIIa–LES above PIP). We further show that a LES-CD separation of ≥3 cm is associated with a near unlikelihood of maintaining a physiological location of the LES below the PIP and indicates a clinically relevant hiatal hernia.

These findings if confirmed by others have significant clinical implications, namely, that any endoscopic or surgical intervention is unlikely to succeed in patients with >3 cm HH without HH repair and crus closure.

Author Contribution:

Shunsuke Akimoto: Study Conception and design, acquisition of data, analysis and interpretation of results, drafting of manuscript, final approval to manuscript

Saurabh Singhal: Writing assistance and revision, Analysis and interpretation, Final Approval

Takahiro Masuda: Writing assistance, interpretation, Final approval

Se Ryung Yamamoto: Acquisition of data, Drafting of article, Final approval

Wendy Jo Svetanoff: Writing assistance and revision.

Sumeet K. Mittal: Study Conception and design, writing assistance, drafting and revisions, analysis and interpretation, Final Approval Supervision.

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Table 1 HRM parameters compared between 16 no reflux patients and 34 reflux patients with Type III EGJ morphology

	All (n=50)	No reflux (n=16, 32%)	Reflux (n=34, 68%)
OL(cm)	2.8[2.2-3.2]	2.9[2.5-3.2]	2.6[2.2-3.2]
AL(cm)	0[0-0.6]	1[0-1.8]*	0[0-0]
LESPI(mmHg cm s)	54.4[7.1-286.4]	73.7[43.6-190.6]	30.4[2.9-324]
LESP(mmHg)	16.4[10.4-26.5]	20.2[14.6-27.7]	16[10.2-21.8]
IRP(mmHg)	8.1[5.6-10]	8.7[6.7-10.7]	7.7[5.4-9.8]
DCI(mmHg cm s)	1586[1073-2406]	1946[991-3275]	1570[1171-2186]

* $p < 0.05$, compared with reflux
OL, overall LES length; AL, abdominal LES length; LESP, lower esophageal sphincter pressure; LESPI, LESP integral; IRP, integrated relaxation pressure; DCI, distal contractile integral.

Table 2
HRM parameters and pH study compared between EGJ-Type 3a and EGJ-Type 3b

	EGJ-Type 3a (n=37, 74%)	EGJ-Type 3b (n=13, 26%)
OL(cm)	2.6[2.2-3.2]	2.9[2.6-3.1]
AL(cm)	0[0-0]**	1.4[0.9-1.8]
LESPI(mmHg cm s)	31.6[2.9-82.4]*	233[104-523]
LESP(mmHg)	14.9[10-19.1]*	26.5[20.6-34.6]
IRP(mmHg)	7.5[5.2-9.3]	9.5[7.4-10.4]
DCI(mmHg cm s)	1401[1073-2018]	2406[1214-3442]
Fraction Time pH (<4)	7.9[4.6-11.7]*	2.6[0.9-6.8]
Fraction Time pH (<4) >4.2%	28(75.7%)*	4(30.8%)
DeMeester Score	26.7[19.9-48]*	11.7[3.7-27.1]
DeMeester Score >14.72	30(81.1%)*	4(30.8%)
pH positive	30(81.1%)*	4(30.8%)

* p <0.05, compared with EGJ-Type 3b, ** p<0.001, compared with EGJ-Type 3b
OL, overall LES length; AL, abdominal LES length; LESP, lower esophageal sphincter pressure; LESPI, LESP integral; IRP, integrated relaxation pressure; DCI, distal contractile integral.

Table 3

HRM parameters compared between no reflux patients and reflux patients in each EGJ type

	EGJ-Type 3a (n=37)		EGJ-Type 3b (n=13)	
	No reflux (n=7, 18.9%)	Reflux (n=30, 81.1%)	No reflux (n=9, 69.2%)	Reflux (n=4, 30.8%)
OL(cm)	2.9[2.3-3.2]	2.6[2.2-3.2]	2.9[2.7-3.1]	2.6[2.1-3.1]
AL(cm)	0[0]	0[0]	1.8[1.3-2]*	0.8[0.7-1.2]
LESPI(mmHg cm s)	44[40-70]	17.3[1-150]	179[65-376]	425[280-598]
LESP(mmHg)	16.3[11.4-19.5]	14.5[9.2-19.1]	26.5[19.6-31.8]	28.2[21.2-39.7]
IRP(mmHg)	7.6[5.9-9.2]	7.2[5.2-9.3]	9.5[7.4-12.1]	9.4[8.2-10.1]
DCI(mmHg cm s)	1234[991-1490]	1570[1171-2186]	2641[2314-3442]	1694[1124-3245]

* $p < 0.05$, compared with reflux in EGJ-Type 3b

OL, overall LES length; AL, abdominal LES length; LESP, lower esophageal sphincter pressure; LESPI, LESP integral; IRP, integrated relaxation pressure; DCI, distal contractile integral.

Legends for Figures

Figure 1
Overall length is defined as the distance between distal and proximal borders of the lower esophageal sphincter (LES). Abdominal LES length is defined as the distance between pressure inversion point and distal border of the LES. LES pressure integral (LESPI) is calculated by enclosing the domain of the LES area during 10 second period using DCI tool with 20mmHg isobaric contour at rest without swallows (reprinted from Hoshino et al. J am Coll Surg, 2011, 743-750).

Figure 2
EGJ-type III that has LES-CD separation >2cm and the inter peak nadir pressure≤ gastric pressure. EGJ-type IIIa has PIP below LES. EGJ-type IIIb has PIP at/above LES.
I and E denote inspiration and expiration respectively.

Figure 3
The separation of LES-CD and pH study. We show the correlation with the length LES-CD and the rate of pH positive patients.

Figure 4
Anatomical depiction of relationship of esophagus, stomach and crural diaphragm.
a) EGJ-type I (no hiatal hernia), b) EGJ-type III (hiatal hernia)

Figure 5
Anatomical depiction of possible relation of peritoneum and EGJ. a) EGJ-type IIIa, b) EGJ-type IIIb – a sac of peritoneum is above LES

Figure 1

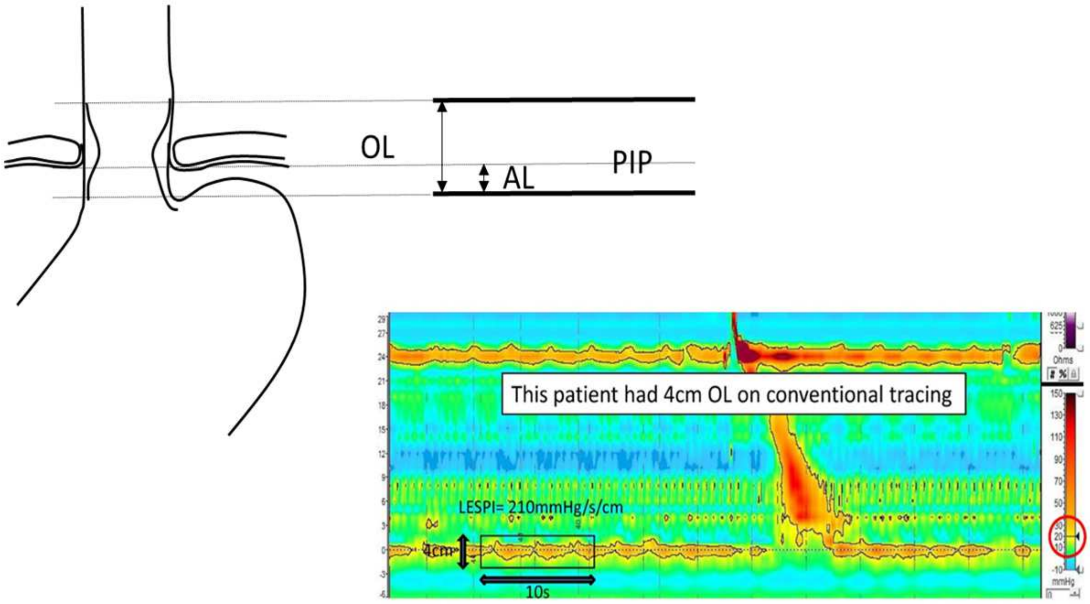
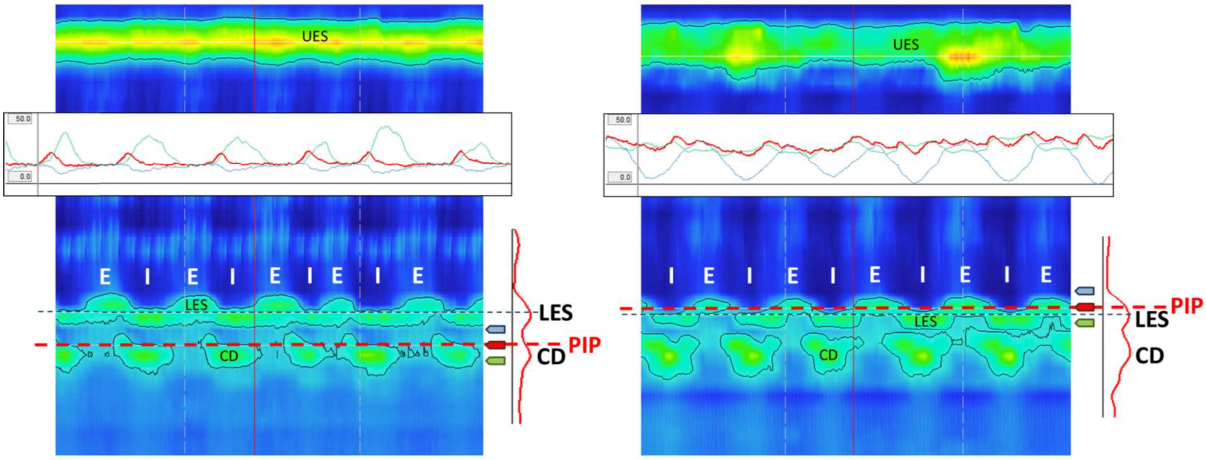

OL
AL
PIP
This patient had 4cm OL on conventional tracing
LESPI= 210mmHg/s/cm
4cm
10s

Figure 2



Type IIIa

Type IIIb

Figure 3

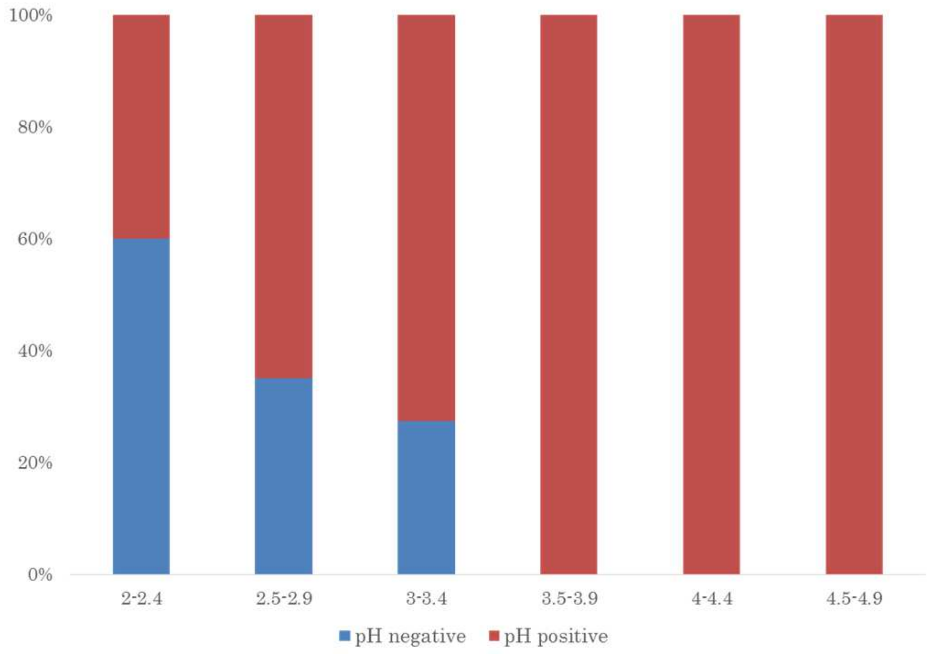

100%
80%
60%
40%
20%
0%
2-2.4
2.5-2.9
3-3.4
3.5-3.9
4-4.4
4.5-4.9
pH negative
pH positive

Figure 4

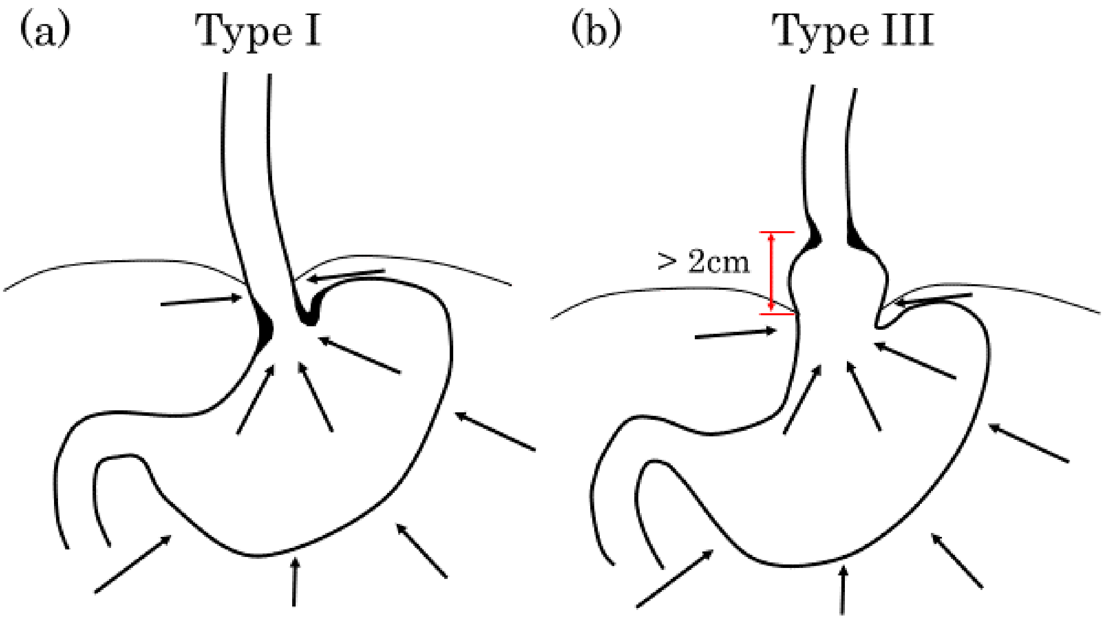


Figure 5