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Orientation of Lower Esophageal Sphincter Pressure Using Three-Dimensional High-Resolution Manometry in Patients with Achalasia: A Pilot Study

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Background: This study was performed to evaluate the orientation of lower esophageal sphincter (LES) pressure in patients with untreated achalasia using three-dimensional high-resolution manometry (3D-HRM).

Methods: The study involved 20 patients with untreated achalasia (10 men, 60 [47-74] years of age). The 3D-HRM assembly had 32 standard channels and 12 3D channels. During basal LES pressure measurements, the orientations of the LES high- and low-pressure zones were evaluated at end-expiration. The directional relationships between the orientation of the LES high- and low-pressure zones were also evaluated.

Results: The LES high-pressure zones were located on the greater curvature side in nine (45%) patients, from the greater curvature to posterior wall side in six (30%), and from the greater curvature to anterior wall side in five (25%). The LES high-pressure zones were located mainly on the greater curvature side, but there were some variations of the orientation among the patients. The LES low-pressure zones were most frequently located from the lesser curvature to the posterior wall side in 11 (55%) patients, from the lesser curvature to anterior wall side in 6 (30%), on the posterior wall side in 2 (10%), and on the anterior wall side in 1 (5%). Significant differences were found in the directional relationships between the orientation of the LES high- and low-pressure zones (P = 0.0053).

Conclusions: This is the first report from Japan focusing on the LES pressure orientation using 3D-HRM. Such evaluation may be useful for clarifying the pathophysiology of achalasia.

(J Nippon Med Sch 2023; 90: 165–172)

Key words: achalasia, lower esophageal sphincter (LES), three-dimensional high-resolution manometry (3D-HRM), esophagogastric junction (EGJ)

Introduction

The lower esophageal sphincter (LES) relaxes during swallowing to allow foods to pass from the esophagus to the stomach and closes at rest to prevent reflux of gastric contents and gastric acid into the esophagus. The LES is formed by the clasp fibers that semi-circumferentially wrap the right side and the sling fibers that form part of the oblique muscles of the stomach and obliquely run from the left side. LES pressure is composed of pressure from these intrinsic smooth muscle sphincters plus pressure from the diaphragm as an external sphincter[1–3]. Previous reports have described evaluation of the orientation of LES pressure using a stepwise pullback technique of a catheter with eight radially oriented pressure transducers[4,5]. More recent reports have described assessment of the orientation of LES pressure using three-dimensional high-resolution manometry (3D-HRM) in which the 3D segment comprises 12 channels of 8 radially dispersed independent pressure sensors[6,7]. According to these studies involving healthy subjects, the horizontal and vertical pressures of the LES are not symmetrical; i.e., the pressure on the left side of the LES (greater cur-

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https://doi.org/10.1272/jnms.JNMS.2023_90-203
Journal Website (https://www.nms.ac.jp/sh/jnms/)

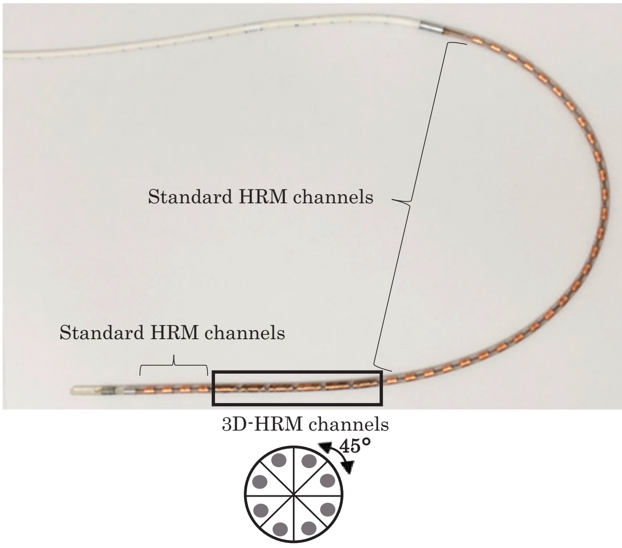

Fig. 1 Photograph of the 3D-HRM assembly. The 4.2-mm outer diameter assembly had the 3D-HRM segment positioned between 28 proximal and 4 distal standard sensing elements spaced 1 cm apart. Each standard channel averaged the pressure signals from the 12 radially dispersed sensors into a single circumferential pressure value. The 3D segment comprised 12 channels of 8 radially dispersed independent pressure sensors with the channels spaced 7.5 mm apart. 3D-HRM: three-dimensional high-resolution manometry

vature of the stomach) is higher than that on the right side (lesser curvature of the stomach)[4,6], and the vertical pressure zone is longer on the right than left side of the LES[4,7]. Studies of the LES pressure orientation in patients with achalasia, a disease characterized by impaired LES relaxation, have also been conducted. Some studies showed that the horizontal pressures of the LES in patients with achalasia were symmetrical using a stepwise pullback technique of a manometry catheter with eight radially oriented pressure transducers[8]. However, other studies using 3D-HRM showed that patients with achalasia have various individual LES pressure asymmetries[7,9]. Therefore, the orientation of LES pressure in patients with achalasia is unclear.

This study was performed to evaluate the orientation of LES pressure in patients with untreated achalasia using 3D-HRM.

Materials and Methods

Patients

Twenty patients with untreated achalasia (10 men, 60 [47-74] years of age) were included in this study. A patient was diagnosed with achalasia according to the Chicago classification ver. 4.0 when the median integrated relaxation pressure (IRP) was ≥15 mmHg and esophageal peristalsis was absent[10]. If the median IRP was <15 mmHg, the patient was comprehensively diagnosed with achalasia when an increase in the intrabolus pressure in the esophagus was observed during the rapid drink challenge (in which 200 mL of water was swallowed continuously) and stagnation of barium in the esophagus was observed by esophagography.

This study was conducted according to the provisions of the Declaration of Helsinki. The study was approved by the Ethics Committee for Human Research of Nippon Medical School (No. 228020).

3D-HRM Assembly

The 3D-HRM assembly (ManoScan 3D; Medtronic plc, Dublin, Ireland) is a solid-state device incorporating a 9.0-cm 3D-HRM segment into an otherwise standard HRM array. In the 4.2-mm outer diameter assembly, the 3D-HRM segment is positioned between 28 proximal and 4 distal standard sensing elements spaced 1 cm apart. Each standard channels averages the pressure signals from the 12 radially dispersed sensors into a single circumferential pressure value. The 3D segment comprises 12 channels of 8 radially dispersed independent pressure sensors with the channels spaced 7.5 mm apart. The 9-cm 3D segment provides 96 independent pressure recordings with a radial resolution of 45° and an axial resolution of 7.5 mm[11] (**Fig. 1**).

Manometry Protocol and Data Analysis

3D-HRM studies were performed after the patients had fasted for at least 6 h. The catheter was placed transnasally and positioned to record from the hypopharynx to the stomach. The catheter was placed in a position where the LES pressure could be measured by the channels of the 3D segment. The manometry protocol included a 1-min period for assessment of the basal LES pressure and 10 swallows of 5 mL of water at 30-s intervals in the supine position.

The 3D-HRM view can be cut open to create a two-dimensional (2D) panoramic view for the data analysis. In the 2D panoramic view, the path of minimum resistance to the bolus flow is determined by the software and denoted using a dotted line, and the highest pressure point on this path is indicated using a red dot (**Fig. 2**). During basal LES pressure measurements, the orientation of the LES high- and low-pressure zones were evaluated at end-expiration, at which time there is little effect of pressure from the diaphragm on LES pressure (**Fig. 2**). The directional relationships between the orientation of the LES high- and low-pressure zones were also evalu-

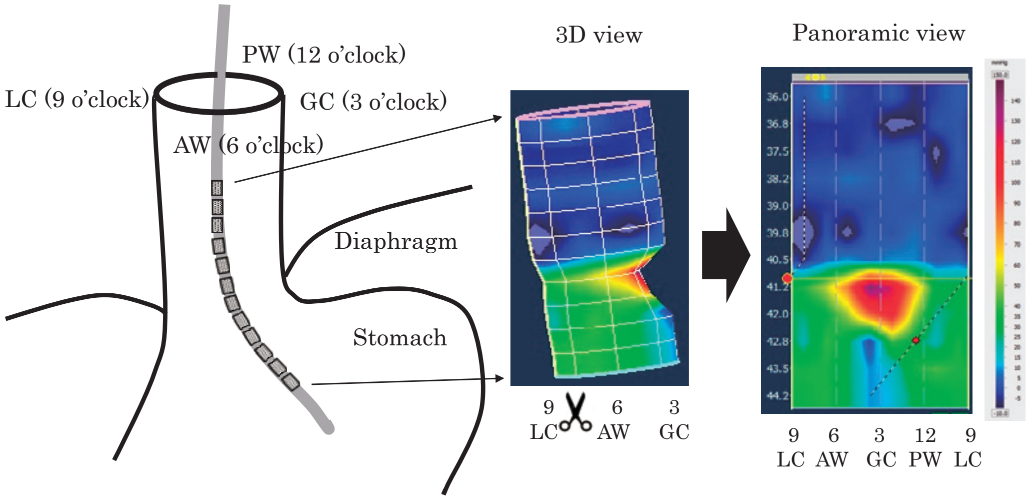

Fig. 2 Schematic representation of the esophagogastric junction as well as the three-dimensional high-resolution manometry view and panoramic view of the esophagogastric junction during deep inspiration. The orientation of the lower esophageal sphincter pressure was determined with the direction of the highest pressure at deep inspiration as the direction of the angle of His; i.e., the greater curvature side of the stomach. GC: greater curvature, LC: lesser curvature, AW: anterior wall, PW: posterior wall

Table 1 Clinical characteristics and demographic data of patients with achalasia

Number of patients	20
Age, years	60 (47–74)
Sex, male/female	10/10
Eckardt score	5 (4–6)
Chicago classification subtype, I/II/III	6/13/1
Basal LESP, mmHg	25.7 (18.0–30.6)
IRP, mmHg	19.8 (14.8–24.7)
Esophagogram subtype, ST/Sig/aSig/NA	10/8/0/2
Esophageal dilatation,<35 mm/35–59 mm/≥60 mm/NA	7/11/0/2

Data are presented as n or median (interquartile range).
IRP: integrated relaxation pressure, LESP: lower esophageal sphincter pressure, ST: straight, Sig: sigmoid, aSig: advanced sigmoid, NA: not available

ated. The orientation of LES pressure was determined with the direction of the highest pressure at deep inspiration as the direction of the angle of His; i.e., the greater curvature side of the stomach[6].

Statistical Analysis

Age, Eckardt score, basal LES pressure, and IRP are expressed as median (interquartile range). The relationships between the orientation of the LES high- and low-pressure zones were evaluated using the chi-square test, and statistical significance was regarded as a *P* value of <0.05.

Results

Patients' Clinical Features

The clinical features and demographic data of the 20 patients with achalasia are shown in **Table 1**. The median Eckardt score was 5 (4-6), and the Chicago Classification subtypes were type I, II, and III in 6, 13, and 1 patient, respectively. The basal LES pressure was 25.7 mmHg (18.0-30.6), and the IRP was 19.8 mmHg (14.8-24.7). The esophagogram subtype and dilatation grading based on the Descriptive Rules for Achalasia of the Esophagus in the Japanese Classification of Achalasia (4th ed.)[12] were straight and sigmoid type in 10 and 8 patients, respectively, and grade I (<35 mm) and II (35-59 mm) in 7 and 11 patients, respectively. Esophagography was not performed in two patients.

Orientations of High- and Low-Pressure Zones of LES

Figure 3 shows examples of the 3D-HRM view and 2D panoramic view, representing the high- and low-pressure zones of the LES at end-expiration. The areas enclosed by

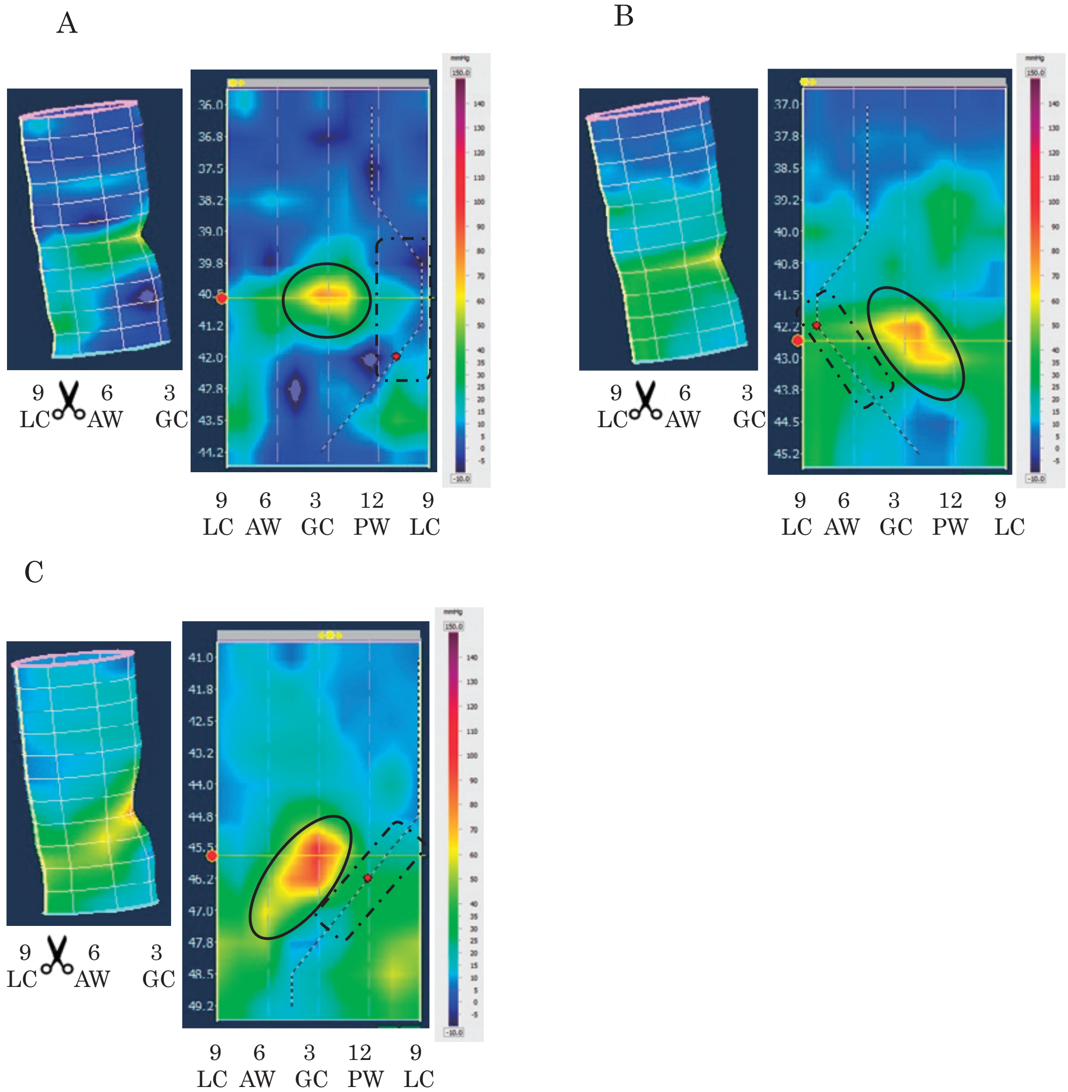

Fig. 3 Examples of three-dimensional high-resolution manometry (3D-HRM) view and panoramic view. (A) 3D-HRM view and panoramic view in which the lower esophageal sphincter (LES) high-pressure zone was on the greater curvature side and the LES low-pressure zone was from the lesser curvature side to the posterior wall side. (B) 3D-HRM view and panoramic view in which the LES high-pressure zone was from the greater curvature side to the posterior wall side and the LES low-pressure zone was from the lesser curvature side to the anterior wall side. (C) 3D-HRM view and panoramic view in which the LES high-pressure zone was from the greater curvature side to the anterior wall side and the LES low-pressure zone was from the lesser curvature side to the posterior wall side. GC: greater curvature, LC: lesser curvature, AW: anterior wall, PW: posterior wall

a solid line indicate the high-pressure zones of the LES, and the areas enclosed by a dashed line indicate the low-pressure zones of the LES. **Figure 3A** shows an example in which the high-pressure zone of the LES is on the greater curvature side and the low-pressure zone of the LES is from the lesser curvature side to the posterior wall side. **Figure 3B** shows an example in which the high-pressure zone of the LES is from the greater curvature side to the posterior wall side and the low-pressure zone of the LES is from the lesser curvature side to the anterior wall side. **Figure 3C** shows an example in which the high-pressure zone of the LES is from the greater curvature side to the anterior wall side and the low-pressure zone of the LES is from the lesser curvature side to the posterior wall side.

The high-pressure zones of the LES at end-expiration were located on the greater curvature side in 9 of 20 patients (45%), from the greater curvature side to the posterior wall side in 6 (30%), and from the greater curvature side to the anterior wall side in 5 (25%) (**Fig. 4**). In all 20

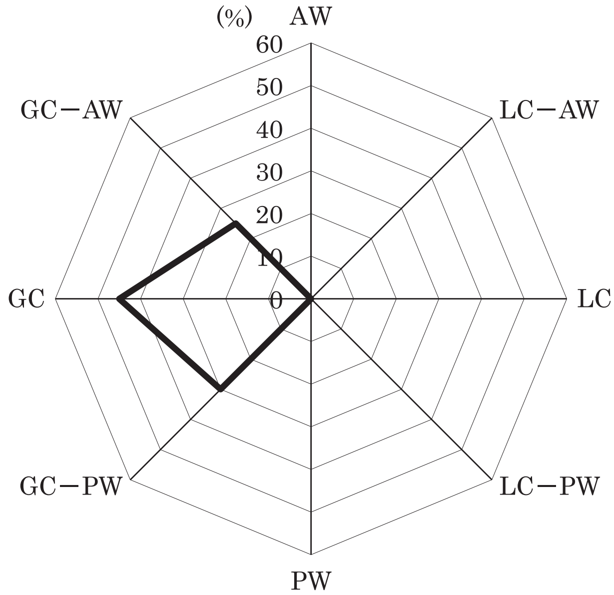

Fig. 4 Orientation of lower esophageal sphincter high-pressure zones at end-expiration. The numbers represent the percentage of patients with each high-pressure zone relative to the total number of patients. GC: greater curvature, LC: lesser curvature, AW: anterior wall, PW: posterior wall

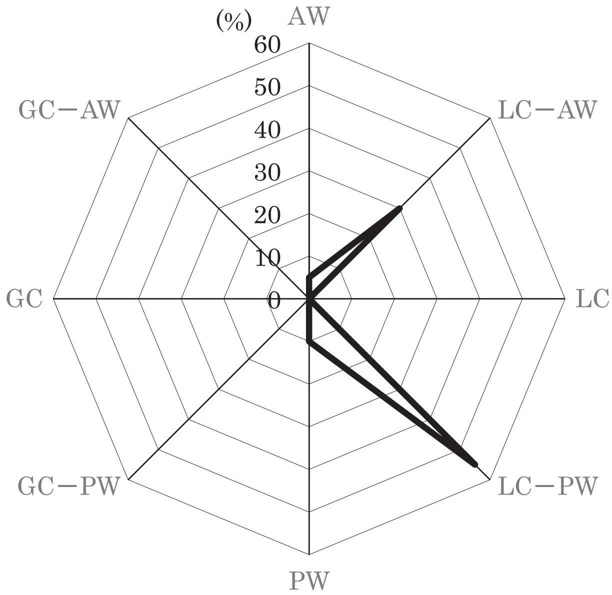

Fig. 5 Orientation of lower esophageal sphincter low-pressure zones at end-expiration. The numbers represent the percentage of patients with each low-pressure zone relative to the total number of patients. GC: greater curvature, LC: lesser curvature, AW: anterior wall, PW: posterior wall

patients, the high-pressure zones of the LES were located mainly on the greater curvature side, but there was some variation in the orientation of the high-pressure zones among the patients.

Conversely, the low-pressure zones of the LES at end-expiration were most frequently located from the lesser curvature side to the posterior wall side in 11 of 20 patients (55%), from the lesser curvature side to the anterior wall side in 6 (30%), on the posterior wall side in 2 (10%), and on the anterior wall side in 1 (5%) (**Fig. 5**).

The relationships between the high- and low-pressure zones of the LES were also analyzed. Of six patients in whom the high-pressure zone was from the greater curvature side to the posterior wall side, the low-pressure zone of the LES was from the lesser curvature side to the anterior wall side in five patients and the anterior wall side in one. By contrast, in all five patients in whom the high-pressure zone of the LES was from the greater curvature side to the anterior wall side, the low-pressure zone of the LES was from the lesser curvature side to the posterior wall side. In addition, of the nine patients in whom the high-pressure zone of the LES was on the greater curvature side, the low-pressure zones of the LES were from the lesser curvature side to the posterior wall side in six patients, on the posterior wall side in two, and from the lesser curvature side to the anterior wall side in one. Significant differences were found in the directional relationships between the orientation of the high- and low-pressure zones of the LES (P = 0.0053) (**Fig. 6**).

Discussion

This is the first report of the orientation of LES pressure using 3D-HRM from Japan. In previous studies using the stepwise pullback technique of a manometric catheter with eight radially oriented pressure transducers, the LES pressure on the left side (greater curvature side) and the posterior wall side of the LES were higher in healthy subjects[4,5]. In the studies using 3D-HRM by Mittal et al.[6,7], the LES pressure was higher on the greater curvature side than lesser curvature side in healthy subjects, and the vertical length of the LES was longer on the lesser curvature side than greater curvature side. Asymmetry of the LES is caused by several factors: the LES is pressed from the left side by the diaphragm, the esophagus bends to the left at the esophagogastric junction (EGJ), and the sling fibers (which form part of the LES) descend obliquely from the angle of His to the lesser curvature of the stomach as the oblique muscle of the stomach. These factors give the LES its unique shape[6,11]. For patients with achalasia, the LES pressure was reported to be uniformly high in all directions[8]. However, a study using 3D-HRM

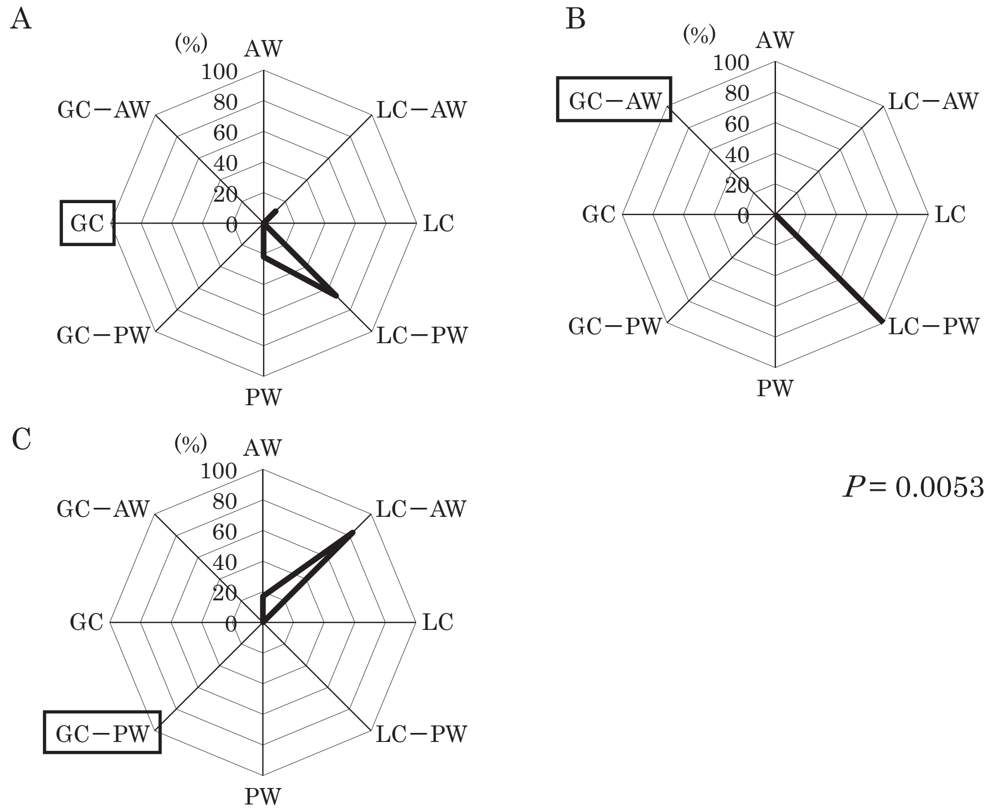

Fig. 6 Directional relationships between the orientation of lower esophageal sphincter (LES) high- and low-pressure zones at end-expiration. The numbers represent the percentage of patients with each LES low-pressure zone relative to the total number of patients. (A) The orientation of LES low-pressure zones for patients in whom the LES high-pressure zone was on the greater curvature side. (B) The orientation of LES low-pressure zones for patients in whom the LES high-pressure zone was from the greater curvature side to the anterior wall side. (C) The orientation of LES low-pressure zones for patients in whom the LES high-pressure zone was from the greater curvature side to the posterior wall side. GC: greater curvature, LC: lesser curvature, AW: anterior wall, PW: posterior wall

in 18 patients with achalasia by Guillaumot et al.[9] revealed that the high-pressure zones of the LES at end-expiration were on the posterior wall side in 8 patients, on the left wall side (greater curvature side) in 3 patients, from the posterior wall side to the left wall side (greater curvature side) in 4 patients, and on the right wall side (lesser curvature side) in 3 patients. Mittal et al.[7] also reported that various LES pressure asymmetries were observed individually in patients with achalasia using 3D-HRM.

Among the components of the LES, the clasp fibers are innervated mainly by inhibitory nerves and relax by the release of nitric oxide, while the sling fibers are innervated mainly by excitatory nerves and relax by the turning off of cholinergic excitation[13]. Thus, because the LES is controlled by both excitatory and inhibitory nerves, different sites and degrees of LES impairment in patients with achalasia may result in various asymmetries of LES pressure on an individual-patient basis. However, our results showed that the high-pressure zones of the LES were mainly located on the greater curvature side, as in healthy subjects, although the high-pressure zones of the LES were closer to the anterior wall of the greater curvature and closer to the posterior wall of the greater curvature on an individual-patient basis. One reason why the orientation of the LES high-pressure zone was less variable among the patients in the present study than among patients in previous reports may be that fewer patients had advanced disease progression.

Previous studies of the orientation of LES pressure revealed that LES pressure on the lesser curvature side was lower than that on the greater curvature side in healthy subjects[4–7]. In the present study of patients with achalasia, the low-pressure zones of the LES were present on the lesser curvature side, as in healthy subjects. In particular, in most patients (12 of 20), the low-pressure zone of the

LES was from the lesser curvature side to the posterior wall side. Furthermore, the directional relationships between the orientations of the LES high- and low-pressure zones revealed that the low-pressure zones of the LES were located on the opposite side of the high-pressure zones in many patients of this study. According to reports describing the circumferential distribution of mucosal breaks in patients with reflux esophagitis, mucosal breaks were most frequently observed from the lesser curvature side to the anterior wall side or from the lesser curvature side to the posterior wall side of the EGJ[14–16]. In addition, studies of the circumferential distribution of Barrett's mucosa also showed that Barrett's mucosa was most frequently observed on the lesser curvature side of the EGJ[17,18]. Studies using catheters with eight radially oriented pH sensors showed that the direction of mucosal breaks in reflux esophagitis and the direction of Barrett's mucosa coincided with the direction of gastroesophageal reflux[19,20]. A possible reason why gastroesophageal reflux is likely to occur on the lesser curvature side is that the LES pressure on the lesser curvature side is low. In addition, because transient LES relaxation, the main mechanism of gastroesophageal reflux, occurs when both the LES and crural diaphragm are relaxed[1], gastroesophageal reflux may be less likely to occur on the greater curvature side because of pressure from the crural diaphragm. In patients with achalasia who develop reflux esophagitis as a complication after peroral endoscopic myotomy (POEM), there may also be a relationship between the direction of the mucosal break and the direction of LES low pressure.

When performing POEM in patients with achalasia, the myotomy is carried out on the posterior or anterior wall, both of which have an anatomical lining, to prevent a postoperative diverticulum[21]. Additionally, when performing a long myotomy from the upper esophagus in patients with type III achalasia, the myotomy is carried out on the posterior wall to prevent a postoperative esophagotracheal fistula[21]. In Heller-Dor myotomy, the myotomy is generally performed on the anterior wall[22]. In addition, the clasp fibers are only cut when aiming to preserve the anti-reflux mechanism, and the sling fibers that contribute to closure of the cardia are cut when the obstruction of the EGJ requires improvement[2]. One of the advantages of POEM is that the direction and length of the myotomy can be freely selected. Additionally, there is a possibility of improving the treatment outcome by selecting the direction of the higher-pressure zone and the longer high-pressure zone of the LES. Evaluation of the horizontal and vertical orientations of the LES pressure using 3D-HRM prior to treatment may help to develop an appropriate treatment strategy for each patient.

This study has three main limitations. First, the orientation of LES pressure was not evaluated in Japanese healthy subjects. Second, 3D-HRM was not performed after treatment of achalasia. Third, this was a pilot study with a small number of patients from a single center. In future studies, it will be necessary to evaluate the orientation of LES pressure in Japanese healthy subjects and compare the orientation of LES pressure before and after POEM and between Chicago classification subtypes in patients with achalasia.

In conclusion, this is the first report from Japan to examine the orientation of LES pressure using 3D-HRM. The high-pressure zones of the LES in patients with achalasia were mainly located on the greater curvature side, but there were some variations in the orientation among the patients. The low-pressure zones were mostly from the lesser curvature side to the posterior wall side. Evaluation of the LES pressure orientation using 3D-HRM in patients with achalasia may be useful for clarifying the pathophysiology of achalasia.

Conflict of Interest: The authors declare that they have no conflict of interest.

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(Received, August 26, 2022)
(Accepted, November 10, 2022)
(J-STAGE Advance Publication, February 21, 2023)