


ORIGINAL ARTICLE

New endoscopic method for gastric hypersensitivity testing: Pilot study

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Key words

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Introduction

The main causes of dyspeptic symptoms in functional dyspepsia (FD) patients are considered to be gastric motility dysfunction^{1–3} and gastric hypersensitivity.⁴ Although there are several tests for gastric motility dysfunction (impaired gastric accommodation^{5–7}) and delayed or rapid gastric emptying^{8–11}), they are only conducted for research purposes. The presence of gastric hypersensitivity was previously evaluated by inserting balloons into the stomach and inflating them¹²; however, this method is invasive. Therefore, there is currently no routine method for evaluating gastric motility dysfunction and gastric hypersensitivity.

Since endoscopy is widespread in Japan, upper gastrointestinal endoscopy is initially performed when dyspeptic symptoms are present to exclude organic diseases, such as ulcers and malignant tumors. We hypothesized that gastric motility dysfunction may be

Abstract

Background and Aim: Although one of the causes of dyspeptic symptoms in functional dyspepsia patients is gastric hypersensitivity, there is currently no routine endoscopic gastric hypersensitivity test. We developed a new endoscopic method for gastric hypersensitivity testing. The aim of the present study was to investigate whether this method is useful for evaluating gastric hypersensitivity in drug-resistant functional dyspepsia patients who were strongly suspected of having gastric hypersensitivity.

Methods: Twenty-seven drug-resistant functional dyspepsia patients and 27 non-functional dyspepsia patients were recruited. Gastric pressure was assessed using an external pressure transducer, and the CO₂ insufflation volume was measured using an endoscopic CO₂-supplied device and flow meter. The following variables were examined: gastric pressure at baseline and gastric pressure, the CO₂ insufflation volume, and compliance of the stomach when patients initially felt abdominal tension following CO₂ insufflation.

Results: No significant differences were observed in baseline gastric pressure or compliance of the stomach between the groups. Drug-resistant functional dyspepsia patients had a significantly smaller CO₂ insufflation volume and lower gastric pressure when symptoms developed than nonfunctional dyspepsia patients. Based on a cutoff value of 1.25 L by receiver operating characteristic curves, sensitivity and specificity for gastric pressure were 85.0 and 96.3%, respectively. Similarly, based on a cutoff value of 12.7 mmHg, sensitivity and specificity for the CO₂ insufflation volume were 81.5 and 81.5%, respectively.

Conclusion: This endoscopic gastric hypersensitivity testing is a useful tool for evaluating the presence of gastric hypersensitivity.

evaluated endoscopically if gastric pressure and the CO₂ injection volume are continuously measured by endoscopy.

We developed a method to measure gastric pressure and the CO₂ injection volume while injecting CO₂ during endoscopy. In the present study, we investigated whether this method is useful for evaluating gastric hypersensitivity using drug-resistant FD patients with frequent and chronic dyspeptic symptoms who were strongly suspected of having gastric hypersensitivity.

Methods

Twenty-seven drug-resistant FD patients and 27 non-FD patients younger than 80 years old were recruited for this case–control study at a single center (Department of Gastroenterology, Nippon Medical School Hospital) between February 2018 and April 2020. All patients were confirmed to have no organic diseases by endoscopy.

Drug-resistant FD patients were defined as those who: (i) did not demonstrate improvements in FD symptoms despite undergoing pharmacological treatments (proton pump inhibitors [PPI], prokinetics, and Kampo medicine) for at least 3 months and subsequently having PPI switched to a potassium-competitive acid blocker for 1 month; (ii) did not have atrophy of the gastric mucosa or a history of *Helicobacter pylori* eradication; and (iii) frequently had FD symptoms before endoscopic examinations. Regarding the scores of the revised F scale,¹³ which is a GERD and FD diagnostic tool, of drug-resistant FD patients before endoscopic examinations, at least 1 dyspeptic symptom score, excluding “belching,” was 4 points (the patient always has dyspeptic symptoms) or greater than 3 points (the patient often has dyspeptic symptoms), and the total dyspeptic symptom score was greater than 8 points. The drug-resistant FD group comprised patients without systemic or metabolic diseases, having negative fecal occult blood test results (2-day method), and no abnormalities on abdominal ultrasonography. Our FD patients were diagnosed with FD based on the criteria of evidence-based clinical guidelines for FD of the Japanese Society of Gastroenterology.¹⁴ Based on the FD diagnostic criteria of the Japanese Society of Gastroenterology, our patient cohort consisted of 20 PDS patients (predominantly PDS symptoms), 4 EPS patients (predominantly EPS symptoms), and 3 PDS + EPS patients (predominantly PDS + EPS symptoms).

Non-FD patients were defined as those with mild reflux esophagitis who did not have gastric mucosal atrophy, a history of *H. pylori* eradication, or any symptoms. The main symptoms of non-FD patients before the PPI treatment were those of reflux, and dyspeptic symptoms were very rare or absent. Reflux symptoms and esophageal mucosal breaks were well-managed by PPI. Regarding the dyspepsia score of the revised F scale of non-FD patients before endoscopic examinations, each dyspeptic symptom score was 1 point (the patient occasionally has dyspeptic symptoms) or less and the total dyspeptic symptom score, excluding “belching,” was 3 points or less.

The revised F scale was used to select patients with frequent upper abdominal symptoms, excluding belching. The reason for excluding “belching” was that it is caused by transient LES relaxation, which is the main mechanism of acid reflux. Therefore, we consider “belching” to be an acid reflux symptom and not a major FD symptom. The presence of gastric mucosa atrophy was evaluated based on the Kimura–Takemoto Classification¹⁵; patients classified as C1 were considered to have no atrophy, whereas those classified as C2–O3 were considered to have atrophy.

The following clinical characteristics were retrospectively examined: body mass index (BMI) and the presence of hiatal hernia. Hiatal hernia was diagnosed if the length between the hiatus and lower margin of the esophageal palisade vessels was greater than 2 cm, and classified into less than and greater than 2 cm.

Endoscopic examinations were performed by the same endoscopist while patients were conscious. The endoscope (H290, Tokyo, Olympus Corp.) was inserted orally and the tip of the scope was placed into the fornix. The tip of the spray tube was then inserted into the forceps channel, and advanced slightly beyond the scope. Gastric juice in the spray tube was flushed with a small amount of air and basal gastric pressure was

measured. Flushing was performed to eliminate clogging caused by gastric juice in the spray tube. When a large amount of liquid was present in the stomach, a small amount was aspirated and an empty space without any liquid was found in order to measure basal gastric pressure. Gastric pressure was measured by considering atmospheric pressure as zero. Breathing was shallow and basal gastric pressure was evaluated as the intermediate pressure of breathing in a stable state. CO₂ was injected at a constant speed (30 mL/s) by pressing the air supply button, and gastric pressure and the CO₂ injection volume were measured. An outline of gastric pressure and CO₂ injection volume measurements is shown in Figure 1. Gastric pressure was measured continuously by connecting the tip of the spray tube to an external pressure transducer (AP-C35, Osaka, Keyence Corp.).

Gastric pressure data were displayed on an endoscopic monitor and stored on a PC using a data collection system (NR-500, NR-HA08, Osaka, Keyence Corp.). The CO₂ injection volume was measured by installing a flow sensor and meter (FD-A10/FD-V40A, Osaka, Keyence Corp) between the CO₂ insertion device (UCR, Tokyo, Olympus Corp.) and the endoscope and was also displayed on the endoscopic monitor, and data were stored on a PC. Patients were instructed to raise their right hand when they noticed a feeling of tension in the upper abdomen during the continuous CO₂ injection, and gastric pressure and the CO₂ injection volume at that time were recorded. The ratio between changes in gastric pressure after the CO₂ injection and CO₂ volume was also calculated as compliance of the stomach. Changes in gastric pressure and CO₂ volume in drug-resistant FD and non-FD patients are shown in Figures 2 and 3, respectively.

In addition, cutoff values were calculated from receiver operating characteristic (ROC) curves of gastric pressure and the CO₂ injection volume at the time of awareness of an initial feeling of tension in both groups, and sensitivity and specificity were calculated. The reproducibility of this endoscopic hypersensitivity testing was assessed after 1 year in 10 non-FD patients whose symptoms did not change during the study period.

Sample size calculations were based on estimating the proportion of patients with gastric hypersensitivity among drug-resistant FD and non-FD patients from ours and previous studies.^{12,16} A previous study reported that 34% of FD patients have gastric hypersensitivity.¹² Our patient population was resistant to PPI and prokinetic agents, which are considered effective for FD. Thus, the effects of gastric hypersensitivity in drug-resistant FD were likely greater than those of drug responsive FD. Based on this observation, we assumed that 50–55% of drug-resistant FD patients also have gastric hypersensitivity. We also found that 10–15% of healthy individuals who did not have gastric symptoms based on our method had gastric hypersensitivity (unpublished data). Thus, in order to calculate the sample size, we assumed that the incidence rates of gastric hypersensitivity in drug-resistant FD and non-FD patients were 55 and 15%, respectively. Based on this assumption, 27 patients in each group were required to detect a difference of at least 40% between groups using Fisher's exact test with a two-sided alpha error of 0.05 and power of 0.80.

Data are presented as medians (25–75 percentiles). The Mann–Whitney *U* test was used to compare differences in age, BMI, gastric pressure, the CO₂ injection volume, and compliance

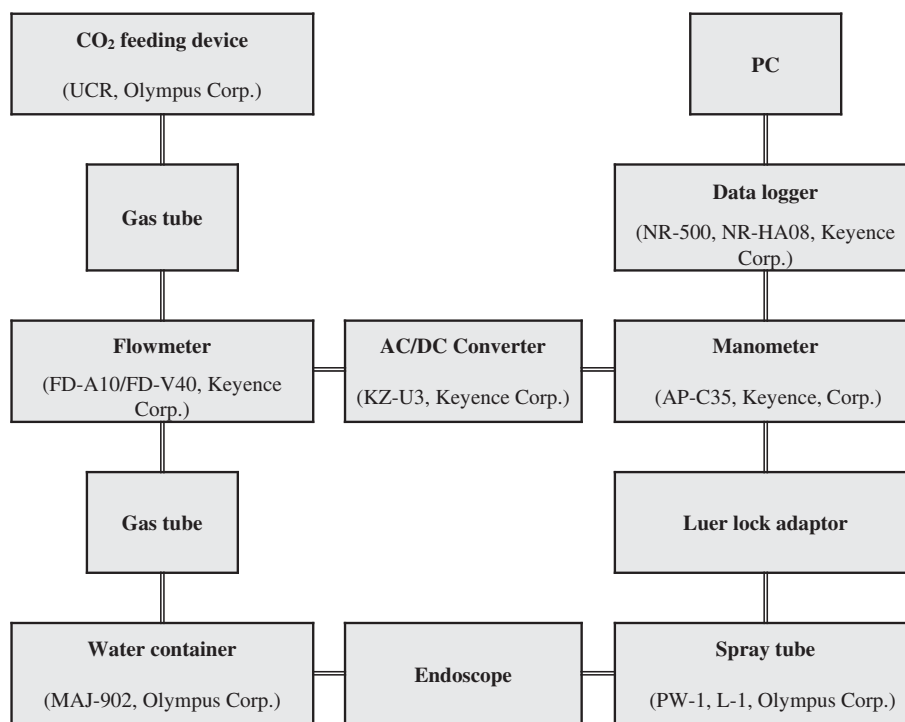


Figure 1 Outline of gastric pressure and CO₂ injection volume measurements.

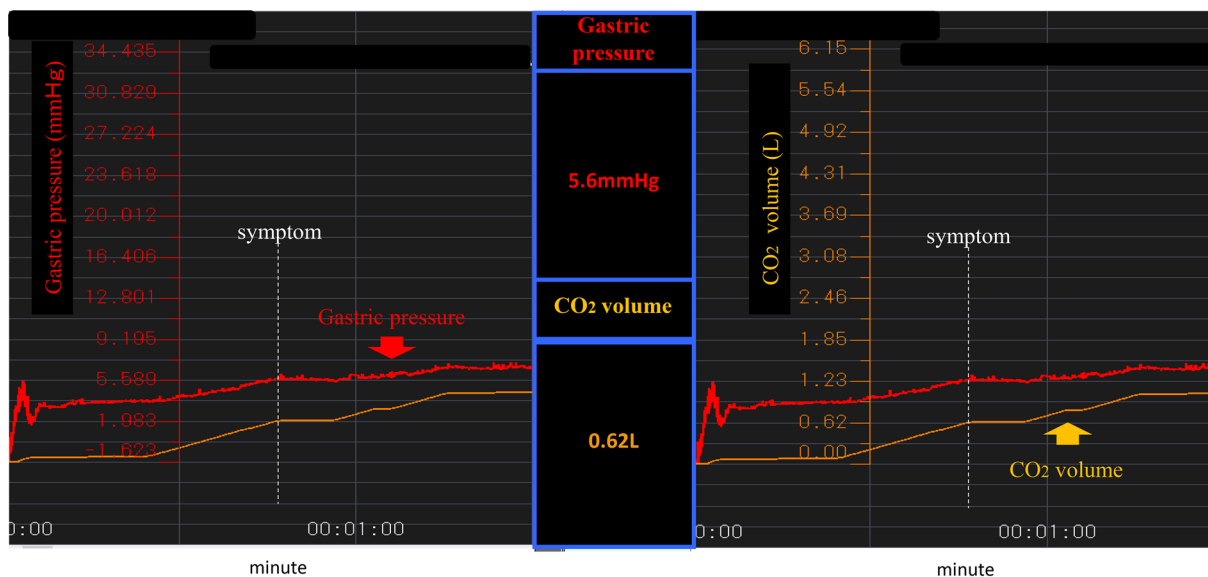


Figure 2 Trace of gastric pressure (red) and the volume of CO₂ (yellow) in a drug-resistant functional dyspepsia (FD) patient. The dotted line indicates the appearance of the symptom, and the column in the center shows the measurements of gastric pressure and CO₂ volume at the time of awareness of an initial feeling of the symptom.

of the stomach between groups. Fischer's exact test was performed to compare sex and hiatal hernia between the groups. The Wilcoxon signed-rank test was performed to compare gastric

pressure and CO₂ injection volume between the first and second measurements of hypersensitivity testing in the non-FD patients. $P < 0.05$ was regarded as significant. Statistical calculations were

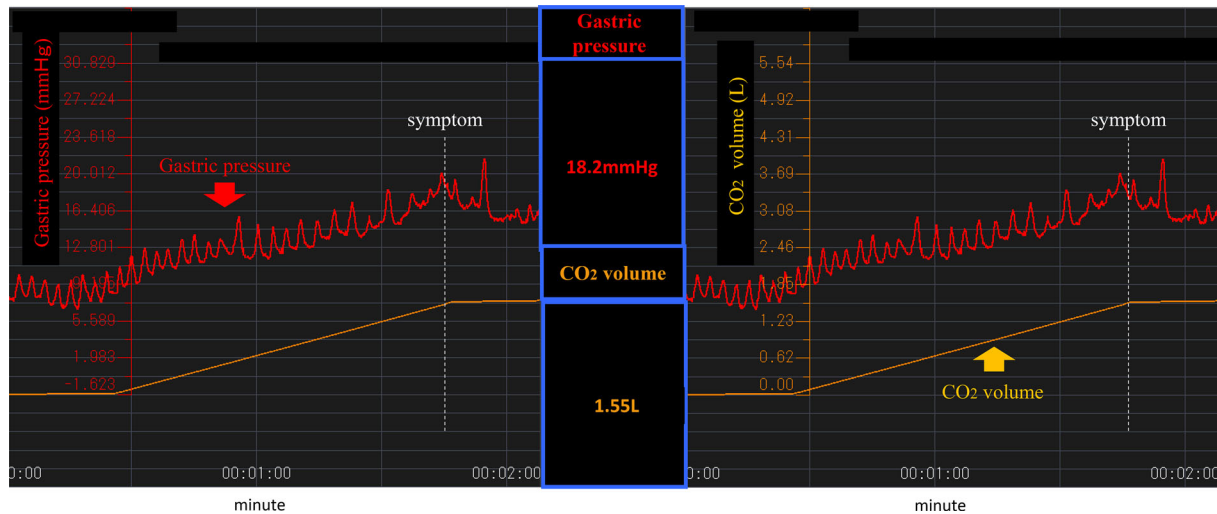


Figure 3 Trace of gastric pressure (red) and the volume of CO₂ (yellow) in a non-functional dyspepsia patient. The dotted line indicates the appearance of the symptom, and the column in the center shows the measurements of CO₂ volume and gastric pressure at the time of awareness of an initial feeling of the symptom.

Table 1 Clinical characteristics and demographic data of patients with drug-resistant functional dyspepsia (FD) and non-FD

	Drug-resistant FD	Non-FD	<i>P</i>
Age (years), median (25–75th percentiles)	57 (48–66)	64 (57–69)	0.091 [†]
Male/Female	9/18	15/12	0.170 [‡]
BMI	20.2 (17.9–23.6)	22.8 (20.0–26.6)	0.018 [‡]
Hiatus hernia +/-	13/14	16/11	0.586 [‡]

[†]The Mann–Whitney *U* test.

[‡]Fischer's exact test.

BMI, body mass index.

performed with IBM SPSS Statistics 25.0 (IBM, Armonk, NY, USA).

This study was performed according to the ethical principles of the Declaration of Helsinki for medical research involving human subjects. The protocol employed was approved by the ethics committee of Nippon Medical School (29-01-881). All subjects gave written informed consent prior to the study.

Results

Clinical characteristics and demographic data. The clinical characteristics of both groups are shown in Table 1. No significant differences were observed in age, sex, or hiatal hernia between the two groups, whereas BMI was significantly lower in the drug-resistant FD group than in the non-FD group.

Basal gastric pressure. No significant differences were noted in basal gastric pressure before the CO₂ injection between the drug-resistant FD (5.6 mmHg [4.6–7.8]) and non-FD (6.3 [5.3–7.4]) groups (*P* = 0.574).

CO₂ injection volume at the time of awareness of a feeling of tension in the upper abdomen during the continuous CO₂ injection. The CO₂ injection volume was significantly lower in the drug-resistant FD group (0.8 L [0.5–0.9]) than in the non-FD group (1.5 [1.3–1.7]) (*P* < 0.0001) (Fig. 4a). The cutoff value calculated from the ROC curve (Fig. 4b) was 1.25 L. Sensitivity based on the cutoff value was 85.0% and specificity was 96.3%.

Gastric pressure at the time of awareness of a feeling of tension in the upper abdomen during the continuous CO₂ injection. The gastric pressure was significantly lower in the drug-resistant FD group (10.7 mmHg [9.5–12.4]) than in the non-FD group (14.5 [13.4–16.9]) (*P* < 0.0001) (Fig. 5a). The cutoff value calculated from the ROC curve (Fig. 5b) was 12.7 mmHg. Sensitivity based on the cutoff value was 81.5% and specificity was 81.5%.

Ratio between changes in gastric pressure and the CO₂ injection volume. No significant difference (*P* = 0.457) was observed in the ratio between changes in gastric pressure between before and after the CO₂ injection and the CO₂

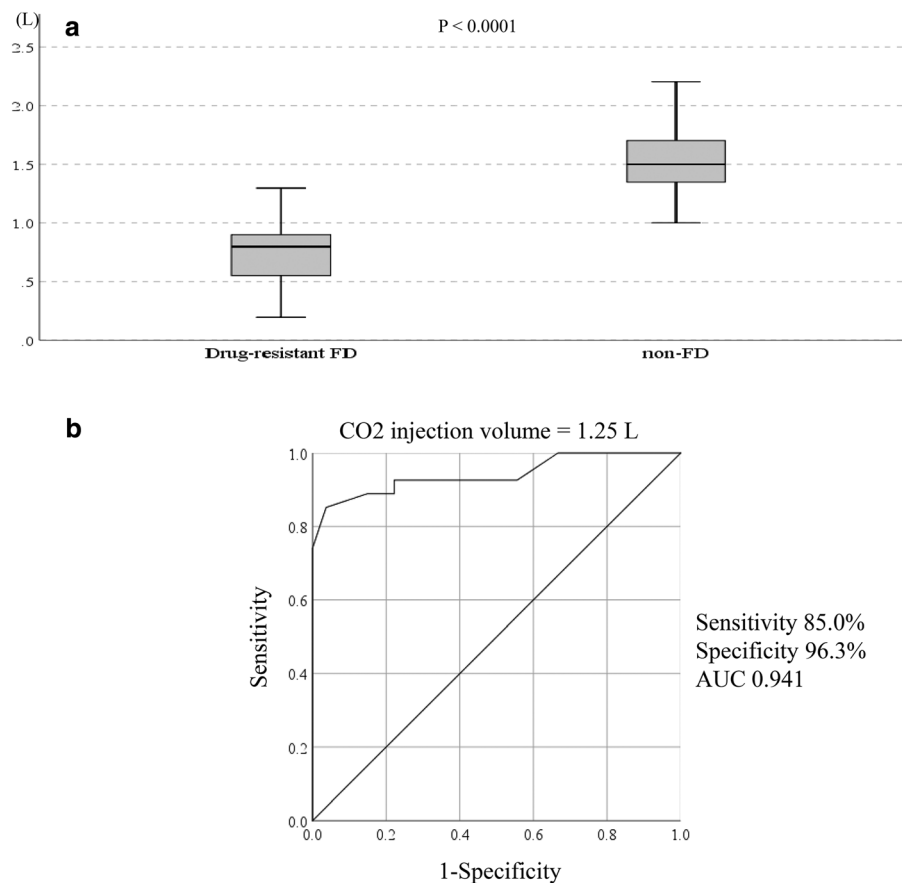


Figure 4 CO₂ injection volume at the time of awareness of a feeling of tension in the upper abdomen during continuous CO₂ injection (a). The optimal cutoff value for gastric hypersensitivity to CO₂ volume was calculated using a receiver operating characteristic (ROC) curve of the CO₂ injection volume (b). FD, functional dyspepsia.

injection volume in either group (resistant group: 6.8 [3.6–8.8], non-FD: 5.1 [4.1–8.3]).

Reproducibility of endoscopic hypersensitivity testing in non-FD patients. In 10 non-FD patients, there was no significant difference in the CO₂ injection volume (first: 1.6 L [1.3–1.9], second: 1.5 [1.3–1.6], $P = 0.4008$) (Fig. 6a) or the gastric pressure (first: 15.6 mmHg [13.6–19.6], second: 15.8 [12.4–18.7], $P = 0.9188$) (Fig. 6b) measured at the time of awareness of a feeling of tension. Our method was highly reproducible, particularly for the measurement of gastric pressure ($P = 0.9188$).

Endoscopic findings. There was no organic disease. In addition, no esophageal mucosal breaks were observed.

Discussion

In the present pilot study, we only selected drug-resistant FD and non-FD patients who did not have atrophy of the gastric mucosa or a history of *H. pylori* eradication because gastric acid and *H. pylori* infection are one of the causes of FD.^{4,17–20} Therefore, the gastric environment was considered to be similar between the

two groups. FD can also be caused by gastric hypersensitivity and gastric motility dysfunction, thus it is treated using acid suppressants aimed at reducing the sensitivity to acid and prokinetic agents. As such, regarding drug-resistant FD, gastric hypersensitivity except for acid plays an important role in drug-resistant FD. We therefore examined our endoscopic method for gastric hypersensitivity testing in drug-resistant FD patients who were likely to have gastric hypersensitivity. Although our patients presented with persistent symptoms, they received FD treatments that may have improved their symptoms. Thus, our patient cohort may not be fully representative of true gastric hypersensitivity in FD. However, most patients reported that the treatments they received were not effective. Therefore, the effects of the treatments were likely limited in drug-resistant FD patients in our study.

The present results revealed that patients in the drug-resistant FD group developed upper abdominal symptoms with a smaller amount of CO₂ and lower gastric pressure than those in the non-FD group. Therefore, there may have been gastric hypersensitivity to pressure and CO₂ volume in the drug-resistant FD group. When the cutoff values for the CO₂ amount and gastric pressure at the time of awareness of a feeling of tension in the upper abdomen during the continuous CO₂ injection were

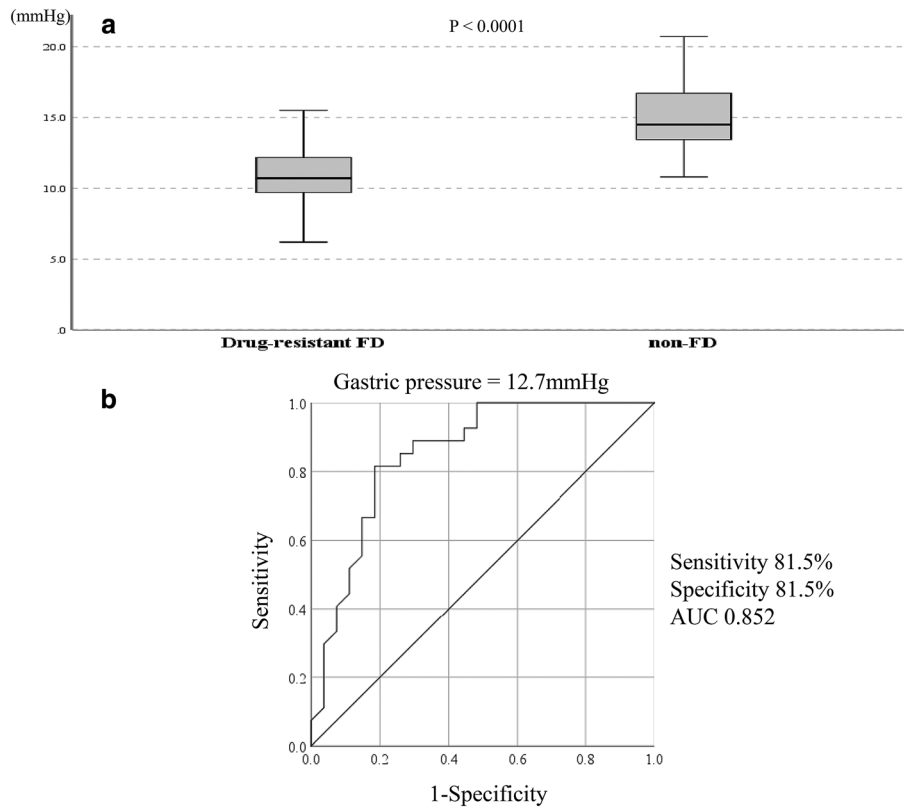


Figure 5 Gastric pressure at the time of awareness of a feeling of tension in the upper abdomen during a continuous CO₂ injection (a). The optimal cutoff value for gastric hypersensitivity to CO₂ volume was calculated using a receiver operating characteristic (ROC) curve of the CO₂ injection volume (b). FD, functional dyspepsia.

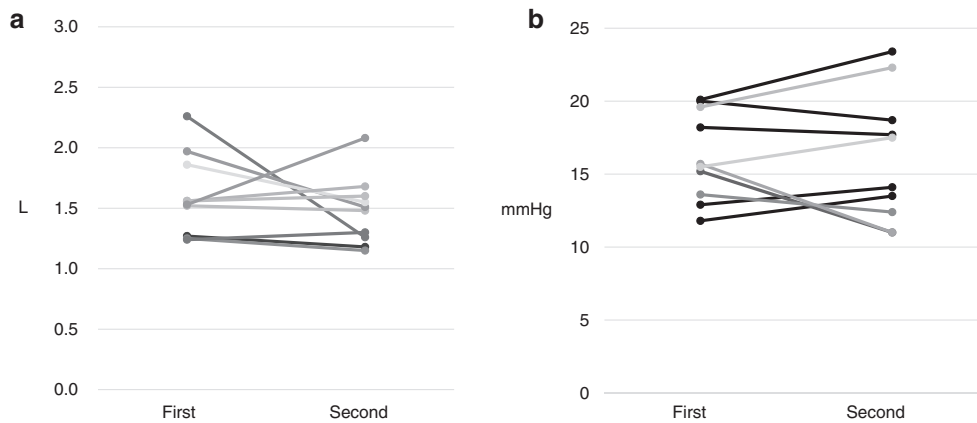


Figure 6 First and second measurements of CO₂ volume (a) and gastric pressure (b) based on the gastric hypersensitivity testing in non-functional dyspepsia patients.

calculated from the ROC curve, sensitivity and specificity were high, particularly for the CO₂ injection volume (sensitivity 85.0% and specificity 96.3%).

Therefore, the endoscopic measurement of the amount of CO₂ injected and gastric pressure may be an index of gastric

hypersensitivity. To the best of our knowledge, this is the first study to demonstrate that gastric hypersensitivity may be evaluated endoscopically. This may become a standard method in the future. Once an inexpensive and durable internal pressure transducer for endoscopy becomes available, further validation is

needed with the external pressure transducer used in the present study. However, this validation is currently not possible because there are no internal pressure transducers that may be inserted endoscopically. Previous findings obtained from high-resolution manometry using an internal pressure transducer²¹ were consistent with our gastric pressure measurements, suggesting that our method of measurement is reliable.

The reproducibility of the measurements is also important to consider. We recruited 10 non-FD patients after 1 year of the initial test to collect additional measurements. They remained asymptomatic over the 1-year period. There was no significant difference between the first and second measurements of gastric pressure and CO₂ injection volume at the time of awareness of a feeling of tension. Thus, our method was highly reproducible, particularly for the measurement of gastric pressure ($P = 0.9188$). This was unable to be tested in drug-resistant FD patients because the degree of symptoms changed over the 1-year period.

In addition to gastric hypersensitivity, impaired gastric compliance may cause FD symptoms with a relatively small CO₂ injection volume. We examined the ratio between changes in gastric pressure and the CO₂ injection volume as an index of gastric compliance. No significant differences were observed in this ratio between the groups, suggesting that the degree of gastric compliance using this method may be equivalent between the groups. As such, gastric hypersensitivity may play an important role in the symptoms observed in the drug-resistant group. Therefore, this endoscopic method may easily and accurately evaluate the presence of gastric hypersensitivity during routine endoscopy.

A barostat is the gold standard in the assessment of gastric hypersensitivity and it was previously reported that 34% of FD patients have gastric hypersensitivity.¹² However, as this method involves insertion of a balloon through the mouth into the stomach, it is a highly invasive technique and is primarily limited for research use. Gastric hypersensitivity is an important factor in the development of FD; therefore, a novel technique that facilitates the measurement of gastric hypersensitivity is required. Our method is minimally invasive because it can be performed at the same time as endoscopy, and is highly specific and sensitive for the detection of hypersensitivity, especially drug-resistant FD. Thus, this method may be useful for investigating the cause of upper abdominal symptoms in the absence of organic disease on endoscopy.

In normal medical care for patients with symptoms of dyspepsia, in the absence of any serious disease, medical care is often completed after endoscopy. After endoscopy, symptoms in some patients are alleviated by the exclusion of organic disease; however, many of the remaining patients express concerns regarding symptoms of an unknown cause. This endoscopic hypersensitivity test may be performed in a short time (approximately 2 min) during normal endoscopy, and may easily detect the presence of gastric hypersensitivity with high sensitivity and specificity. If gastric hypersensitivity is detected in patients, a physician may explain that gastric hypersensitivity is a potential cause of symptoms. By providing such details, physicians can build a stronger relationship with their patients. In addition, this method may be effective in identifying drug-resistant FD during endoscopy and may be used to evaluate the efficacy of the treatment for patients with gastric hypersensitivity. Future studies will

focus on addressing the clinical use of this method in greater detail.

Patients with mild reflux esophagitis were selected as non-FD patients in the present study. Although an overlap between FD and reflux esophagitis has been reported, the main symptoms of patients with mild reflux esophagitis were heartburn and regurgitation, which are not FD symptoms, and these reflux symptoms were well-managed by PPI. Therefore, mild reflux esophagitis does not overlap with FD. The only difference in the backgrounds of both groups was BMI. Regarding BMI in FD patients, although there is currently no consistent conclusion,^{22,23} BMI was significantly lower in the drug-resistant FD group than in the non-FD group in the present study. One of the causes of low BMI may be that patients in the drug-resistant group did not consume a sufficient amount of food due to severe FD symptoms. Another cause may be that patients in the non-FD group had reflux esophagitis, which results in a higher BMI than in healthy subjects.²⁴

The present study was limited in that it was a single-center study performed by the same endoscopist using a small number of drug-resistant FD patients based on the Japanese Society of Gastroenterology criteria. To establish this testing method in the future, it will be necessary to evaluate differences in results among endoscopists and due to the frequency and type of symptoms as well as age. It is also important to evaluate the usefulness of this test for FD patients based on the Rome IV criteria²⁵ and the reproducibility of the test, in addition to validating gastric pressure measurement using an internal pressure transducer and calculating the cutoff level based on the measurements collected from healthy individuals.

In conclusion, drug-resistant FD patients developed abdominal symptoms at a smaller CO₂ volume and lower gastric pressure than non-FD patients, and sensitivity and specificity for the CO₂ injection volume and gastric pressure calculated from the ROC curve were high. This new endoscopic test is a useful tool for evaluating the presence of gastric hypersensitivity.

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