Title: Efficacy of rikkunshito in patients with functional heartburn: a prospective pilot study

Running title: Rikkunshito for functional heartburn

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Abstract

Background: Although the efficacy of rikkunshito in patients with treatment-resistant non-erosive gastroesophageal reflux disease (NERD) has been reported, it is unclear for which subgroups of NERD patients (per the Rome IV criteria) rikkunshito is effective. The objective of this study was to investigate the efficacy of rikkunshito in patients with functional heartburn.

Methods: Ten patients with functional heartburn who experienced symptoms of dyspepsia were enrolled. The patients were administered rikkunshito for 8 weeks. The frequency scale for the symptoms of GERD (FSSG), Japanese translation of quality of life in reflux and dyspepsia questionnaire (QOLRAD-J), and hospital anxiety and depression scale (HADS) were evaluated before and 4 and 8 weeks after administration. Overall treatment efficacy (OTE) was evaluated 8 weeks after administration.

Results: One patient was discontinued 4 weeks after administration because of voluntary withdrawal. Total FSSG score was significantly ($P = 0.039$) lower 8 weeks after treatment or at discontinuation (13.2 ± 8.0) than before treatment (18.3 ± 10.7). Although QOLRAD-J score tended to increase 8 weeks after treatment or at discontinuation compared with before treatment, no significant difference was observed. HADS score did not decrease significantly 8 weeks after treatment or at discontinuation.

compared with before treatment. However, a correlation was found between total FSSG and HADS anxiety scores (correlation coefficient: 0.684, $P = 0.027$).

Conclusions: This was the first study to investigate the efficacy of rikkunshito in patients with functional heartburn. Rikkunshito may be effective in these patients.

Keywords: rikkunshito, functional heartburn, non-erosive gastroesophageal reflux disease, potassium-competitive acid blocker-resistant, multichannel intraluminal impedance-pH monitoring

Introduction

Approximately 60% of patients with gastroesophageal reflux disease (GERD) have non-erosive GERD (NERD). According to the Rome IV criteria (the most recent international criteria for functional gastrointestinal disorders), NERD is classified into subgroups as follows: true NERD with excessive esophageal acid exposure, reflux hypersensitivity with normal esophageal acid exposure and reflux-related symptoms, and functional heartburn with normal esophageal acid exposure and symptoms unrelated to reflux¹. Functional heartburn is a cause of proton pump inhibitor (PPI)-resistant NERD, and it was reported that around 20%–50% of patients with PPI-resistant NERD have functional heartburn^{2–5}. Additionally, approximately half of NERD patients who are resistant to potassium-competitive acid blocker (P-CAB) (novel and potent acid secretion inhibitor), and whose symptoms do not improve, have functional heartburn^{6–8}. Although the pathophysiology of functional heartburn is unclear, the appearance symptoms is not triggered by reflux. Rather, it is believed symptoms are caused by visceral hypersensitivity, abnormal recognition processing in the brain, and changes in esophageal perception because of psychological factors such as stress and anxiety^{1,9–11}. Functional heartburn has also been reported to overlap with functional dyspepsia (FD) and irritable bowel syndrome^{12–14}.

According to Rome IV, antidepressants such as tricyclic antidepressants, serotonin reuptake inhibitors, serotonin noradrenergic reuptake inhibitors, and other neuromodulators (i.e., pregabalin or gabapentin) may relieve the symptoms of functional heartburn¹. Furthermore, the psychological approach is effective in some patients. However, overall therapeutic satisfaction is low and symptoms are refractory in many patients with functional heartburn. In practice, treating functional heartburn in patients with GERD is a problem. The Japanese GERD clinical practice guidelines describe administration of the Japanese herbal medicine, rikkunshito, as a therapeutic option for refractory GERD¹⁵. Rikkunshito exerts many pharmacological actions such as promoting gastric emptying^{16,17} and gastric adaptive relaxation^{18–20}, and suppressing upper gastrointestinal hypersensitivity^{21,22}. Moreover, the efficacy of rikkunshito in patients with PPI-resistant NERD has been reported. However, no reports have examined in detail the efficacy of rikkunshito in the different subgroups of NERD per the Rome IV criteria. The objective of this pilot study was therefore to explore the efficacy of rikkunshito in patients with functional heartburn.

Methods

Patients

The enrollment period was September 2017 to December 2018, and a total of 10 patients (mean age: 54.3 ± 17.2 years, four males) diagnosed with functional heartburn who experienced symptoms of dyspepsia were enrolled. This was a prospective, single-arm, and open-label study (UMIN000029668). Patients with symptoms of dyspepsia and GERD such as heartburn and regurgitation despite administration of P-CABs (20 mg/day vonoprazan), for ≥ 2 weeks and with ≥ 8 points according to the frequency scale for the symptoms of GERD (FSSG) (including ≥ 1 point in acid-related dysmotility symptom [ARD] score [dyspepsia-related symptom score]) were examined by esophagogastroduodenoscopy and high-resolution manometry (HRM), to exclude organic diseases and primary esophageal motility disorders. After excluding these diseases, multichannel intraluminal impedance-pH (MII-pH) monitoring was performed during P-CAB therapy to examine the relationship between reflux and symptoms. Patients were diagnosed with functional heartburn when esophageal acid exposure was normal (percentage of time with esophageal pH < 4 was $< 4\%$) and symptom index (SI) was $< 50\%$. The Starlet ver. 8.1–15.3 (Starmedical, Inc. Tokyo, Japan) HRM system was used and diagnosis was determined according to the Chicago Classification v3.0, which is an HRM-based classification of esophageal motility disorders²³. Exclusion criteria were as follows: reflux esophagitis of grade A or more severe per the modified Los

Angeles classification, eosinophilic esophagitis, peptic ulcers, malignant tumors, primary esophageal motility disorders, abnormal esophageal acid exposure, SI of $\geq 50\%$ in MII-pH monitoring, prior surgery of the upper gastrointestinal tract, other organic digestive disorders, pregnancy and lactation, and administration of Japanese herbal medicines within 4 weeks before administration of rikkunshito.

Study protocol

Patients were administered rikkunshito (7.5 g/day) for 8 weeks and the FSSG (including total, reflux symptom [RS], and ARD scores) was evaluated as the primary endpoint before and 4 and 8 weeks after administration²⁴. As secondary endpoints, the Japanese translation of quality of life in reflux and dyspepsia questionnaire (QOLRAD-J) (including total, emotional distress, sleep disturbance, eating/drinking disorders, physical/social functioning, and vitality scores)²⁵ and hospital anxiety and depression scale (HADS) (including total, anxiety, and depression scores)²⁶ were evaluated before and 4 and 8 weeks after administration, and overall treatment efficacy (OTE) was evaluated before and 8 weeks after administration. Additionally, correlations between the primary and secondary endpoints were evaluated. Concomitant use of the following drugs was prohibited during the study period: gastric acid secretion inhibitors (PPI/histamine-2 receptor antagonist/P-CAB), Japanese herbal medicines, anxiolytics,

antipsychotics, antidepressants, mood stabilizers, psychostimulants, neuromodulators (i.e., pregabalin or gabapentin), and nonsteroidal anti-inflammatory drugs. Furthermore, the following drugs were permitted to be used in combination as concomitantly restricted drugs throughout the study period, although changes in administration method or dose or new administration were forbidden: prokinetic drugs, gastrointestinal motility inhibitors, stomachics/digestants, and corticosteroids (excluding topical drugs). As safety assessment, blood tests (aspartate aminotransferase, alanine transferase, gamma-glutamyl transpeptidase, alkaline phosphatase, total bilirubin, potassium, creatinine, and blood urea nitrogen) were performed before and 8 weeks after administration, and edema and adverse events were confirmed 4 and 8 weeks after administration.

This study was performed in accordance with the provisions of the Declaration of Helsinki and was approved by the Ethics Committee for Human Research of Nippon Medical School. All patients provided written informed consent.

The frequency scale for the symptoms of gastroesophageal reflux disease (FSSG)

The FSSG is a questionnaire for diagnosing GERD and assessing the response to therapy. The FSSG can assess both reflux- and dyspepsia-related symptoms, and consists of 12 items. Seven relate to reflux symptoms, while five relate to dyspeptic symptoms. The total score is calculated by summing the RS and ARD scores, and total

scores of more than 8 were considered to indicate probable GERD, as previously validated²⁴.

Japanese translation of quality of life in reflux and dyspepsia questionnaire (QOLRAD-J)

QOLRAD-J is a disease-specific quality of life (QOL) assessment instrument that consists of 25 questions across five domains: emotional distress, sleep disturbance, eating/drinking disorders, physical/social functioning, and vitality. The QOL of each domain is represented by a score from 1 to 7. Lower QOLRAD-J score indicated poorer GERD-related QOL²⁵.

The hospital anxiety and depression scale (HADS)

The HADS is used to assess anxiety and depression and is divided into anxiety and depression subscales. Each subscale contains seven items that are scored from 0 to 3, which result in a total subscale score from 0 to 21. Higher HADS score indicates increased tendency toward anxiety and depression. The recommended cutoff score for diagnosing anxiety and depression is ≥ 8 for each subscale²⁶.

Overall treatment efficacy (OTE)

The OTE questionnaire is a seven-point scale that rates changes in symptoms as follows: highly improved, improved, slightly improved, unchanged, slightly aggravated,

aggravated, or highly aggravated.

High-resolution manometry (HRM)

HRM studies were performed following a fast of at least 6 h. The Starlet HRM system has a catheter with 36 solid-state sensors at 1-cm intervals (Unisensor AG, Attikon, Switzerland). The catheter was placed transnasally and positioned to record from the hypopharynx to the stomach. The manometric protocol included a 5-min period to assess basal lower esophageal sphincter pressure and 10 swallows of 5 mL of water at 30-s intervals in the supine position. The presence or absence of primary esophageal motility disorders was diagnosed based on the Chicago Classification v3.0²³. The normal cutoff value of each parameter with the Starlet system was determined by referring to examination values from healthy subjects.

Multichannel intraluminal impedance-pH (MII-pH) monitoring

Twenty-four-hour MII-pH monitoring was performed using a Sleuth multichannel intraluminal impedance ambulatory system (Sandhill Scientific, Inc., Highlands Ranch, CO, USA). At the end of the 24-h recording period, data were transferred and analyzed manually using dedicated software (BioView® analysis; Sandhill Scientific, Inc.). Meal periods were marked and excluded from the analysis. Liquid-containing reflux episodes (liquid only and mixed gas-liquid) were identified based on previously described criteria

as a retrograde 50% decline in impedance from baseline in at least two sites²⁷. Similarly, gas-only reflux episodes were identified as a simultaneous increase in impedance >5,000 ohms in at least two esophageal-measuring segments²⁷. Reflux episodes were characterized according to pH measurements as acidic, weakly acidic, or weakly alkaline according to a published consensus report on detection and definition of gastroesophageal reflux²⁸. Symptoms were considered to be associated with liquid reflux if an episode of liquid reflux was detected 5 min prior to the symptom occurring. The relationship between gas-only reflux and symptoms was investigated for each reflux and symptom episode. The SI was calculated for each patient in relation to liquid or gas reflux and was defined as the number of symptoms associated with reflux divided by the total number of symptoms²⁹. SIs were assessed for each individual symptom if patients recorded different types of symptoms.

Statistical analysis

Age; body mass index; acid exposure time; number of reflux episodes; SI; distal contractile integral (DCI), distal latency, and integrated relaxation pressure (IRP) values; and FSSG, QOLRAD-J, and HADS scores are presented as mean $\pm$ standard deviation. Statistical analysis of therapeutic effects was performed using the paired t-test or Wilcoxon signed rank test for changes in measured values obtained at each

evaluation point. Additionally, the relationship between the primary and secondary endpoints was examined using Pearson's or Spearman's rank correlation coefficient. $P < 0.05$ was considered statistically significant.

Results

Clinical and demographic parameters

Clinical and demographic parameters of the 10 patients with functional heartburn are shown in Table 1. One patient was discontinued 4 weeks after administration of rikkunshito because of voluntary withdrawal. No patients experienced adverse events. According to MII-pH monitoring, mean esophageal acid exposure time was $0.01 \pm 0.03\%$, and most reflux episodes on administration of 20 mg/day vonoprazan were weakly acidic reflux. Mean SI was $3.8\% \pm 9.30$. According to HRM, mean DCI was $1,278.73 \pm 1,303.40$ mmHg-s-cm and mean IRP was 11.92 ± 6.02 mmHg.

FSSG, QOLRAD-J, and HADS scores, and OTE

Regarding the FSSG, total score was significantly ($P = 0.039$) lower 8 weeks after treatment or at discontinuation (13.2 ± 8.0) than before treatment (18.3 ± 10.7). RS and ARD scores tended to be decreased 8 weeks after treatment or at discontinuation (RS: 7.5 ± 4.2 , ARD: 5.7 ± 4.7) compared with before treatment (RS: 10.8 ± 6.4 , ARD: $7.5 \pm$

4.9), although no significant differences were observed (RS: $P = 0.053$, ARD: $P = 0.117$) (Figure 1).

Regarding the QOLRAD-J, total score, and scores for emotional distress, sleep disturbance, eating/drinking disorders, physical/social functioning, and vitality tended to be increased 8 weeks after treatment or at discontinuation compared with before treatment. However, no significant differences were observed (before treatment vs. 8 weeks after treatment or at discontinuation, total: 5.26 ± 1.12 vs. 5.61 ± 1.16 , $P = 0.264$; emotional distress: 4.60 ± 1.63 vs. 5.17 ± 1.81 , $P = 0.234$; sleep disturbance: 5.40 ± 1.33 vs. 5.58 ± 1.49 , $P = 0.797$; eating/drinking disorders: 5.40 ± 1.24 vs. 5.72 ± 1.04 , $P = 0.299$; physical/social functioning: 5.80 ± 0.93 vs. 6.10 ± 0.94 , $P = 0.164$; vitality: 5.13 ± 1.36 vs. 5.53 ± 1.43 , $P = 0.320$) (Figure 2).

Regarding the HADS, total and depression scores tended to be decreased 8 weeks after treatment or at discontinuation, although no significant differences were observed, and anxiety score did not change (before treatment vs. 8 weeks after treatment or at discontinuation, total: 9.10 ± 5.49 vs. 8.90 ± 7.77 , $P = 0.496$; anxiety: 5.10 ± 3.21 vs. 5.10 ± 4.56 , $P = 0.961$; depression: 4.00 ± 3.02 vs. 3.80 ± 3.58 , $P = 0.813$) (Figure 3).

Regarding the OTE at 8 weeks after treatment, one patient was improved, three were slightly improved, five remained unchanged, and one was not assessable because of

discontinuation (Figure 4).

Correlation between changes in FSSG and QOLRAD-J scores

Regarding correlations between changes in FSSG and QOLRAD-J scores from 8 weeks after treatment or discontinuation to before treatment, correlations existed between total FSSG score and total QOLRAD-J, emotional distress, and sleep disturbance scores (total FSSG vs. total QOLRAD-J: correlation coefficient (r) = -0.669 , $P = 0.032$; total FSSG vs. QOLRAD-J emotional distress: $r = -0.738$, $P = 0.012$; total FSSG vs. QOLRAD-J sleep disturbance: $r = -0.652$, $P = 0.039$).

Correlations existed between FSSG RS and total QOLRAD-J, emotional distress, and sleep disturbance scores (FSSG RS vs. total QOLRAD-J: $r = -0.639$, $P = 0.045$; FSSG RS vs. QOLRAD-J emotional distress: $r = -0.731$, $P = 0.014$; FSSG RS vs. QOLRAD-J sleep disturbance: $r = -0.669$, $P = 0.032$). Correlations were also found between FSSG ARD score and total QOLRAD-J, emotional distress, eating/drinking disorders, and vitality scores (FSSG ARD vs. total QOLRAD-J: $r = -0.728$, $P = 0.014$; FSSG ARD vs. QOLRAD-J emotional distress: $r = -0.659$, $P = 0.036$; FSSG ARD vs. QOLRAD-J eating/drinking disorders: $r = -0.753$, $P = 0.010$; FSSG ARD vs. QOLRAD-J vitality: $r = -0.861$, $P = 0.001$) (Figure 5).

Correlation between changes in FSSG and HADS scores

Regarding correlation between changes in FSSG and HADS scores from 8 weeks after treatment or discontinuation to before treatment, a correlation existed between total FSSG and HADS anxiety scores ($r = 0.684$, $P = 0.027$) (Figure 6). No correlations were found between FSSG RS and HADS scores or between FSSG ARD and HADS scores.

Correlation between changes in FSSG score and OTE

Regarding correlation between changes in FSSG score from 8 weeks after treatment or discontinuation to before treatment and OTE, correlations were found between total FSSG score and OTE, and between FSSG RS score and OTE (total FSSG vs. OTE: $r = 0.857$, $P = 0.0017$; FSSG RS vs. OTE: $r = 0.857$, $P = 0.0017$) (Figure 7).

Discussion

This is the first report to examine the efficacy of rikkunshito in patients with functional heartburn. Prior studies have examined the efficacy of rikkunshito in patients with PPI-resistant GERD and NERD. Tominaga et al. compared administration of 10 mg/day rabeprazole (RPZ) plus rikkunshito vs. administration of double dose of RPZ (20 mg/day) in patients with PPI-resistant GERD, and found significant decreases in total FSSG scores in both groups after 4 weeks³⁰. Furthermore, Tominaga et al. compared administration of 10 mg/day RPZ plus rikkunshito with administration of 10

mg/day RPZ plus placebo in patients with PPI-resistant NERD, and found that patients administered RPZ plus rikkunshito showed significant improvements in mental QOL score compared with those administered RPZ plus placebo³¹. However, these studies were conducted in patients with GERD and NERD with various etiologies, and no subgroup analysis was performed in patients with functional heartburn. None have been conducted in patients with functional heartburn. In the present study, significant improvement in total FSSG score was observed after administration of rikkunshito, indicating it may be effective in patients with functional heartburn. In the DREAM study, which previously compared rikkunshito with placebo in patients with FD, those administered rikkunshito showed significant improvement in modified-FSSG score compared with those administered placebo. Furthermore, total HADS and anxiety scores decreased in the group administered rikkunshito, indicating an association between improvement in psychiatric symptoms and improvement in symptoms of GERD in response to rikkunshito³². Rikkunshito was reported to suppress increases in serum adrenocorticotrophic hormone and cortisol under stress conditions³³, and is believed to have the potential to improve disturbance of autonomic nerves caused by psychological stress. In patients with functional heartburn, stress and anxiety may increase esophageal hypersensitivity and induce symptoms. Therefore, in this study,

rikkunshito was also expected to improve psychiatric symptoms in patients with functional heartburn. However, no significant improvements in HADS scores were observed following its administration, although positive correlation was found between changes in total FSSG and HADS anxiety scores, and an association between improvement in symptoms of GERD and psychiatric symptoms was found. A possible explanation for the lack of significant improvement in HADS scores in the present study (unlike the DREAM study) is that pretreatment mean total HADS, anxiety, and depression scores were originally low at 9.1, 5.1, and 4.0 points, respectively.

Although no significant changes were observed in QOLRAD-J scores following administration of rikkunshito, correlations were observed between changes in total FSSG and RS scores, and total QOLRAD-J, emotional distress, and sleep disturbance scores. Regarding the relationship between GERD and sleep disorders, it was reported that reflux at night causes sleep disorders, and sleep disorders cause esophageal hypersensitivity³⁴. Our results showed an association between symptoms of GERD and quality of sleep in patients with functional heartburn.

In the present study, patients with P-CAB (20 mg/day vonoprazan)-resistant NERD were selected over those with PPI-resistant NERD for diagnosing functional heartburn because patients with PPI-resistant NERD may experience symptoms caused by acid

reflux induced by insufficient gastric acid suppression on administration of PPI.

Contrarily, in a previous study, no patients had symptoms caused by acid reflux on administration of P-CAB⁶. Therefore, patients with functional heartburn can be more readily selected from those with P-CAB-resistant NERD. Vonoprazan may be used to determine whether symptoms are caused by acid reflux or other by administering it at 20 mg for 2–4 weeks (P-CAB test).

This study had limitations. This was a single-arm study with a small number of patients, and it was unclear why rikkunshito was effective in patients with functional heartburn. However, our results were valuable for newly exploring the efficacy of rikkunshito in patients with functional heartburn. Future placebo-controlled comparative studies with large sample sizes are necessary to further validate our results. In addition to patients with functional heartburn, it is necessary to investigate the efficacy of rikkunshito in patients with true NERD who experience excessive esophageal acid exposure and in patients with reflux hypersensitivity with appearance of symptoms triggered by reflux.

In conclusion, to our knowledge, this was the first study to investigate the efficacy of rikkunshito in patients with functional heartburn, and according to our results, it may be effective in these patients.

Author's disclosure of potential Conflicts of Interest (COI).

Dr. Iwakiri received lecture fees from Otsuka Pharmaceutical Co., Ltd. and Takeda Pharmaceutical Co., Ltd. There are no other conflicts of interest to declare.

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Figure Legends

Figure 1. Frequency scale for symptoms of gastroesophageal reflux disease (FSSG) scores before (0 weeks) and 4 and 8 weeks after administration of rikkunshito

A: Total, B: Reflux symptom (RS), C: Acid-related dysmotility symptom (ARD)

Figure 2. Japanese translation of quality of life in reflux and dyspepsia questionnaire (QOLRAD-J) scores before (0 weeks) and 4 and 8 weeks after administration of rikkunshito

A: Total, B: Emotional distress, C: Sleep disturbance, D: Eating/drinking disorders, E: Physical/social functioning, F: Vitality

Figure 3. Hospital anxiety and depression scale (HADS) scores before (0 weeks) and 4 and 8 weeks after administration of rikkunshito

A: Total, B: Anxiety, C: Depression

Figure 4. Overall treatment efficacy (OTE) at 8 weeks after treatment

N/A: Not available

Figure 5. Correlation between changes in frequency scale for the symptoms of gastroesophageal reflux disease (FSSG) and Japanese translation of quality of life in reflux and dyspepsia questionnaire (QOLRAD-J) scores

A: Total FSSG vs. total QOLRAD-J, B: Total FSSG vs. QOLRAD-J emotional distress,

C: Total FSSG vs. QOLRAD-J sleep disturbance, D: FSSG reflux symptom (RS) vs.

total QOLRAD-J, E: FSSG RS vs. QOLRAD-J emotional distress, F: FSSG RS vs.

QOLRAD-J sleep disturbance, G: FSSG acid-related dysmotility symptom (ARD) vs.

total QOLRAD-J, H: FSSG ARD vs. QOLRAD-J emotional distress, I: FSSG ARD vs.

QOLRAD-J eating/drinking disorders, J: FSSG ARD vs. QOLRAD-J vitality

r: correlation coefficient

Figure 6. Correlation between changes in total frequency scale for the symptoms of gastroesophageal reflux disease (FSSG) and hospital anxiety and depression scale

(HADS) anxiety scores

r : correlation coefficient

Figure 7. Correlation between changes in frequency scale for the symptoms of gastroesophageal reflux disease (FSSG) score and overall treatment efficacy (OTE)

OTE scale results were classified as follows: 1: highly improved, 2: improved, 3: lightly improved, 4: unchanged, 5: lightly aggravated, 6: aggravated, 7: highly aggravated.

A: Total FSSG vs. OTE, B: FSSG reflux symptom (RS) vs. OTE

r : correlation coefficient

Fig. 1

Fig. 2

Fig. 2

A

B

C

Fig. 3

Fig. 4

Fig. 5

Fig. 5

Fig. 5

Fig. 6

Fig. 7

Table 1. Clinical and demographic features of patients with functional heartburn

Number of patients	10
Age, years	54.3 ± 17.2
BMI	21.2 ± 2.6
Sex, male/female	4/6
Current alcohol use, n	2
Current smoking, n	3
<i>H. pylori</i> infection, n	4
Modified LA classification, grade M/N	3/7
MII-pH monitoring parameters	
Esophageal acid exposure time (%)	0.01 ± 0.03
Total number of reflux episodes	21.9 ± 16.54
Number of acid reflux episodes	0.7 ± 1.57
Number of weakly acidic reflux episodes	20.8 ± 15.23
Number of weakly alkaline reflux episodes	0.5 ± 1.27
SI (%)	3.8 ± 9.30
HRM parameters	
DCI (mmHg-s-cm)	1278.73 ± 1303.40
DL (seconds)	6.43 ± 0.98
IRP (mmHg)	11.92 ± 6.02

Data presented as mean ± standard deviation, BMI: body mass index, *H. pylori*: *Helicobacter pylori*, LA: Los Angeles, MII-pH: multichannel intraluminal impedance-pH, SI: symptom index, HRM: high-resolution manometry, DCI: distal contractile integral, DL: distal latency, IRP: integrated relaxation pressure