Pathophysiological classification of functional dyspepsia using a novel drinking-ultrasonography test

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Abstract

Background: Functional dyspepsia (FD) is heterogeneous disease characterized by various upper abdominal symptoms. The major mechanism of FD symptoms includes impaired fundic accommodation, delayed gastric emptying, and visceral hypersensitivity. We developed a novel drinking-ultrasonography to combine drink test with ultrasonography to assess gastric motility and sensory function of FD patients.

Method: Subjects were sixty successive FD patients according to the Rome III criteria. A drinking-ultrasonography test was performed after subjects had fasted. The subjects ingested 200 ml of water at two-minute intervals four times (total, 800 ml) through a straw. The maximum cross-section of the proximal stomach was visualized before water intake, after each water intake, and 5 and 10 minutes after the completion of drinking using extracorporeal ultrasonography. Abdominal symptoms were evaluated using the visual analog scale (VAS) a total of 5 times. Normal range of cross-sectional area and VAS were set using average±2 standard deviations of 33 healthy volunteers. Cases outside normal range were diagnosed with motor or sensory disorder.

Results: The drinking-ultrasonography test classified FD patients into four groups without adverse effect or trouble. The distribution of each group were 27% in normal group, 15% in impaired relaxation group, 10% in delayed emptying group, and 48% in

visceral hypersensitivity group. There was no significant correlation between the pathophysiological classification and subtypes of FD defined by the Roma III criteria.

Conclusion: We developed a novel drinking-ultrasonography test that was effective in classifying FD patients according to pathophysiological features.

Introduction

Functional dyspepsia (FD) is a clinical condition characterized by various upper abdominal symptoms, such as postprandial fullness, early satiation, epigastric pain or burning, marked by the absence of organic, systemic, or metabolic disease that would explain the symptoms. Recently, the Rome III committee proposed new diagnostic criteria for functional gastrointestinal disorders including FD[1)]. Rome III divided FD into two categories according to predominant dyspeptic symptoms: postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS). However, the two subtypes overlap greatly. Heterogeneity of FD symptoms depends on different pathophysiological features. The major mechanism of FD symptoms includes impaired fundic accommodation, delayed gastric emptying, and visceral hypersensitivity, as well as other complicating factors[2)3)]. It seems likely that understanding of pathophysiology in different types of FD patients is required for different management approaches.

Tests of gastric motility and sensory function are available in clinical practice. Gastric barostat is regarded as the gold standard for the measurement of gastric accommodation[4)5)]. However, it is not widely used because the procedure is extremely invasive. Imaging methods such as single photon emission computer tomography

(SPECT), or magnetic resonance imaging (MRI), or scintigraphy have also been occasionally reported[6)-9)]. These tests also can not be used extensively because of radiation exposure and long examination time. On the other hand, ultrasonography, which is safe, non-invasive, and inexpensive allows the direct observation of gastric movements[10)-12)]. In addition, a drink test has recently been developed for the evaluation of sensory function[13)-15)]. We combined a similar drink test of our own design with ultrasonography to assess gastric motility and sensory function of FD patients in term of pathophysiological classification.

Subjects and Methods

1) Subjects

Sixty successive subjects that had been diagnosed as FD according to the Rome III criteria at Hokkaido University Hospital between August 2006 and December 2008 were enrolled in this study. Subjects with a mean age of 50.0 years consisted of 14 males and 46 females. All subjects had one or more of these symptoms for the previous 3 months: postprandial fullness, early satiation, epigastric pain or burning. All subjects underwent upper gastrointestinal endoscopy and abdominal ultrasonography to exclude organic abdominal disease. Normal control included 33

healthy volunteers without any abdominal symptoms, pregnancy, or history of gastrointestinal diseases.

This study was approved by the ethics committee of Hokkaido University Hospital, and written informed consent was obtained from all subjects.

2) Basic procedure

A drinking-ultrasonography test was performed after subjects had fasted for at least 6 hours. Subjects were supine, and ingested water through a straw that was placed at facial height so that they raised themselves minimally. Commercially available water in PET bottles (Alkali Ion Water®, Kirin, Tokyo) and graduated plastic cups were used.

During the drinking period, the subjects ingested 200 ml of water at two-minute intervals four times (total, 800 ml). When they felt unable to ingest more, the test was discontinued. Examination of emptying period was conducted at 5 and 10 minutes after the completion of drinking 800ml (or discontinuation), at which point the test concluded.

3) Evaluation of the gastric cross-sectional area

All ultrasonographic examinations were performed using an Aplio™ XV (Toshiba, Tokyo) and a 3.5-MHz convex-type probe (375BT) by one ultrasonography technician with more than 20 years of experience.

The cross-section of the proximal stomach was visualized by extracorporeal ultrasonography via the 10th intercostal space using the spleen as an echo window. The maximum cross-section of the proximal stomach was visualized before water intake, after each water intake at 2-minute intervals, and 5 and 10 minutes after the completion of the drinking test. After the image was frozen, the mucosal surface of the gastric lumen was traced using the ultrasonography system, and the cross-sectional area was calculated. Static and animated images were stored on hard disk.

We set normal range of cross-sectional area of the proximal stomach using average±2 standard deviations (SD) of 33 healthy volunteers. All cross-sectional areas of healthy volunteers were plotted inside of normal range within 8 minutes of drinking period[16]. FD patients were diagnosed with impaired relaxation, if cross-sectional area fell within the normal range within 8 minutes (Figure 1a). All healthy volunteers showed that 5- and 10-minute marks of the emptying period fell the maximum last mark of drinking period[16]. FD patients were diagnosed with delayed emptying, if the cross-sectional area at 5- and 10-minute marks of the emptying period exceeded the

cross-sectional area at the end of the drinking period (Figure 1b).

4) Evaluation of symptoms

During the drinking period, abdominal symptoms were evaluated using the visual analog scale (VAS) a total of 5 times, as well as before the test and immediately after each ingestion of water. Abdominal symptoms before the test were used as the baseline. Subjects were asked about difficulty in drinking due to symptoms such as abdominal fullness and epigastric pain, During the test, they filled out a questionnaire by themselves using a numerical scale of 0 (no difficulty) to 10 (most difficult).

The normal range was set to within two SD of the average VAS score of the control subjects. All VAS scores f healthy volunteers were plotted inside of normal range within 8 minutes of drinking period[16]. FD patients are diagnosed with visceral hypersensitivity, if their VAS score plotted over normal range within 8 minutes of drinking period (Figure 1c).

5) Statistical analysis

The distribution of PDS and EPS in each group was compared to evaluate the relationship between pathophysiological classification and subtypes of Rome III criteria.

Fisher exact test was performed to compare the distribution of PDS and EPS in three groups with that of normal group using SPSS software (version 11.0 for Microsoft Windows). A result of $p<0.05$ was considered significant.

Results

The drinking-ultrasonography test was performed on all patients without adverse effect or trouble. The results were classified into four groups: normal, impaired relaxation, delayed emptying, and visceral hypersensitivity. Nine FD patients were diagnosed with both impaired relaxation and visceral hypersensitivity. These patients were classified into impaired relaxation group. Overall, there were 16 FD patients in normal group, 9 in impaired relaxation group, 6 in delayed emptying group, and 26 in visceral hypersensitivity group (Figure 2). The distribution were 27% in normal group, 15% in impaired relaxation group, 10% in delayed emptying group, and 48% in visceral hypersensitivity group.

The relationship between pathophysiological classification and subtypes of Rome III criteria (i.e., PDS and EPS) was evaluated. The impaired relaxation group consisted of 7 PDS and 2EPS. The delayed emptying group consisted of 7 PDS and 2EPS. The visceral hypersensitivity group consisted of 14 PDS and 2 EPS. The

normal group consisted of 9 PDS and 7 EPS (Table 1). There was no significant correlation between the two classifications.

Discussion

We developed a novel drinking-ultrasonography test and classified patients with FD into four pathophysiological groups. In this drinking-ultrasonography test, a drink load is given at equal intervals, the cross-sectional area of the fornix is measured, and symptoms are verbally assessed at each interval. This approach allows the simultaneous evaluation of gastric relaxation, sensory function, and gastric emptying. It seems that the greatest benefit of drinking-ultrasonography test is its non-invasive nature, ease of use, tolerability, and short duration (under 20 minutes) for patients. Recently, minimally invasive tests of gastric motility and sensory function such as ultrasonography, ^{13}C- octanoic acid urea breath test, and drink test have been reported. These tests are able to evaluate gastric relaxation, gastric emptying, gastroduodenal reflux, or visceral hypersensitivity. However, these minimally invasive tests don’t detect simultaneously both gastric motor disorder and sensory disorder. The drinking-ultrasonography test does not require radiation, expensive chemical substance, and unusual equipment. In terms of money and time saving, this novel test is useful

for routine examination of dyspeptic patients.

To develop the drinking-ultrasonography test, we examined adequate interval time, tidal volume, and total volume of water intake. Preliminary trail confirmed that gender, age, and BMI were unrelated to the results of this test[16]. FD patients showed low water intake, poor increase in the cross-sectional area of the fornix, and rapid increase of severity of upper abdominal symptoms such as epigastric discomfort and gastric pain after water intake compared with healthy control[16]. In particular, there was significant difference in gastric relaxation.

The pathophysiological mechanisms of FD include motility disorders, perception disorders, acid hypersensitivity, psychological factors, *H. pylori* infection, duodenal dysfunction and abnormalities within the brain-gut axis. Effective treatment depends on the specific pathophysiological condition of each FD patient. In general practice, prokinetic drugs or anti-secretary acid drugs have been empirically used as a first line for the treatment of FD. The drinking-ultrasonography test makes it possible to identify pathophysiology-based subgroup. In this study, half of FD patients revealed gastric sensory disorder. On the other hand, 25% of FD patients revealed neither motility nor sensory disorder of stomach. Delayed gastric emptying has long been considered the main pathology of FD and extensively studied. In this study, delayed

gastric emptying was detected in only 10% of FD patients. Recent studies have shown that the incidence of delayed gastric emptying is about 25%[17)18)], and many studies have suggested no association between delayed gastric emptying and specific symptoms. Until now, no data have been available on the physiological features of the categories EPS or PDS as defined by the Roma III. We found no association between EPS or PDS subgroup and pathophysiological features diagnosed with this novel test. EPS and PDS were a mixture of different pathophysiological features. Further study is necessary to clarify the relationship between the pathophysiological classification using this novel test and the strategy of FD treatment.

Conclusion

We developed a novel test by combining a drink test with ultrasonography to classify FD patients according to pathophysiological features. The drinking-ultrasonography test is adequate for evaluating gastric motility and sensory function.

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Figure legend

Figure 1

These are cases of impaired relaxation, delayed emptying, and visceral hypersensitivity. Cases outside normal range were diagnosed with motor or sensory disorder.

Figure 2

The distribution of FD patients were 16/70(27%) in normal group, 9/60(15%) in impaired relaxation group, 6/60(10%) in delayed emptying group, and 29/60(48%) in visceral hypersensitivity group.

Disclosure Statement

The author declares that no financial or other conflict of interest exists in relation to the content of the article.

Table 1 Relationship between pathophysiological group and FD subtypes

Group	n	PDS	EPS	Odds ratio (95%CI)	*P*
Normal	16	9 (56%)	7 (44%)	1.0	
Visceral hypersensitivity	29	14 (48%)	15 (52%)	0.73 (0.21-2.5)	0.39
Impaired relaxation	9	7 (78%)	2 (22%)	2.72 (0.43-17.4)	0.90
Delayed emptying	6	3 (50%)	3 (50%)	0.78 (0.12-5.1)	0.92

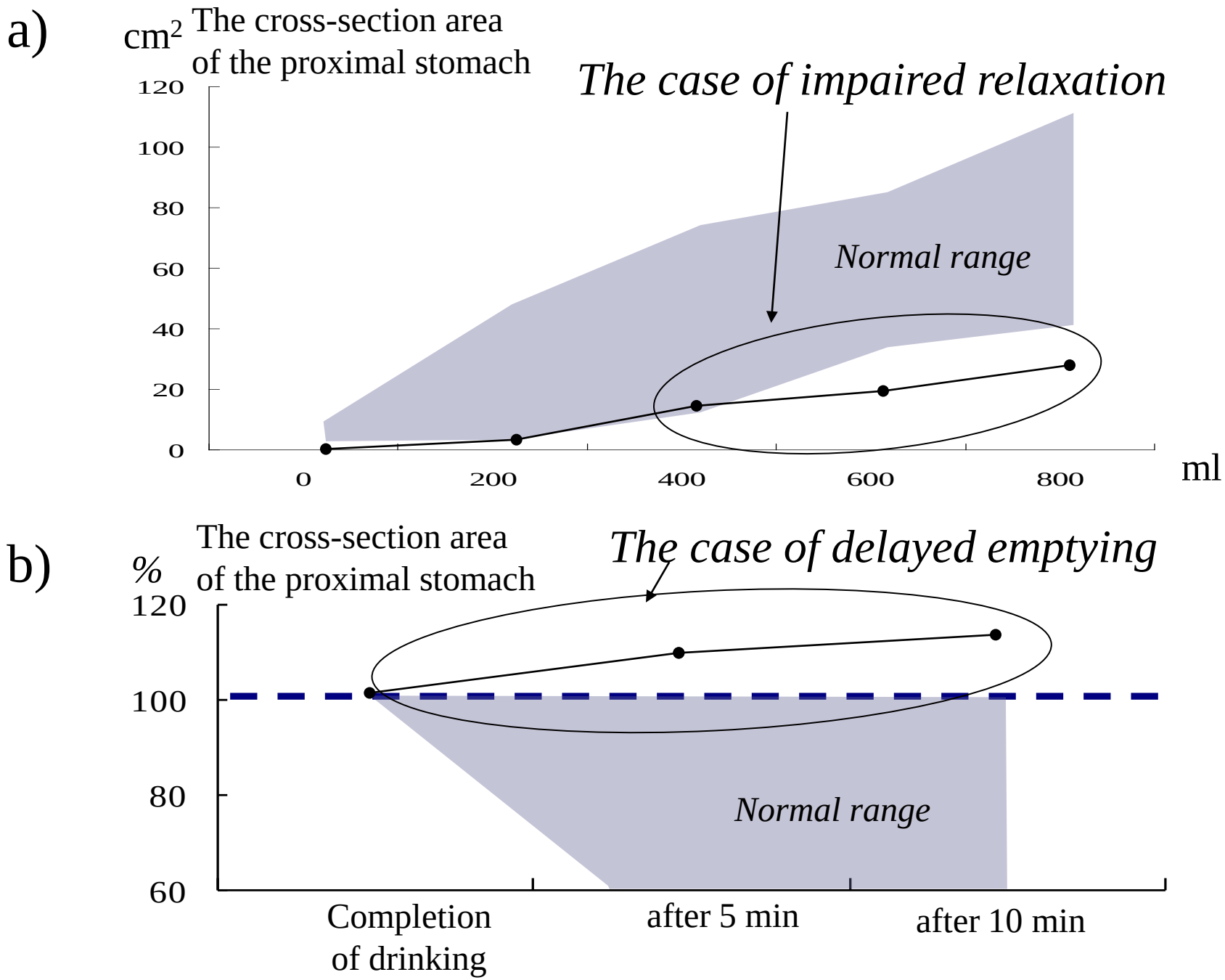
a)
cm2
The cross-section area
of the proximal stomach
The case of impaired relaxation
Normal range
120
100
80
60
40
20
0
0
200
400
600
800
ml
b)
%
The cross-section area
of the proximal stomach
The case of delayed emptying
120
100
80
60
Normal range
Completion
of drinking
after 5 min
after 10 min

Figure 1

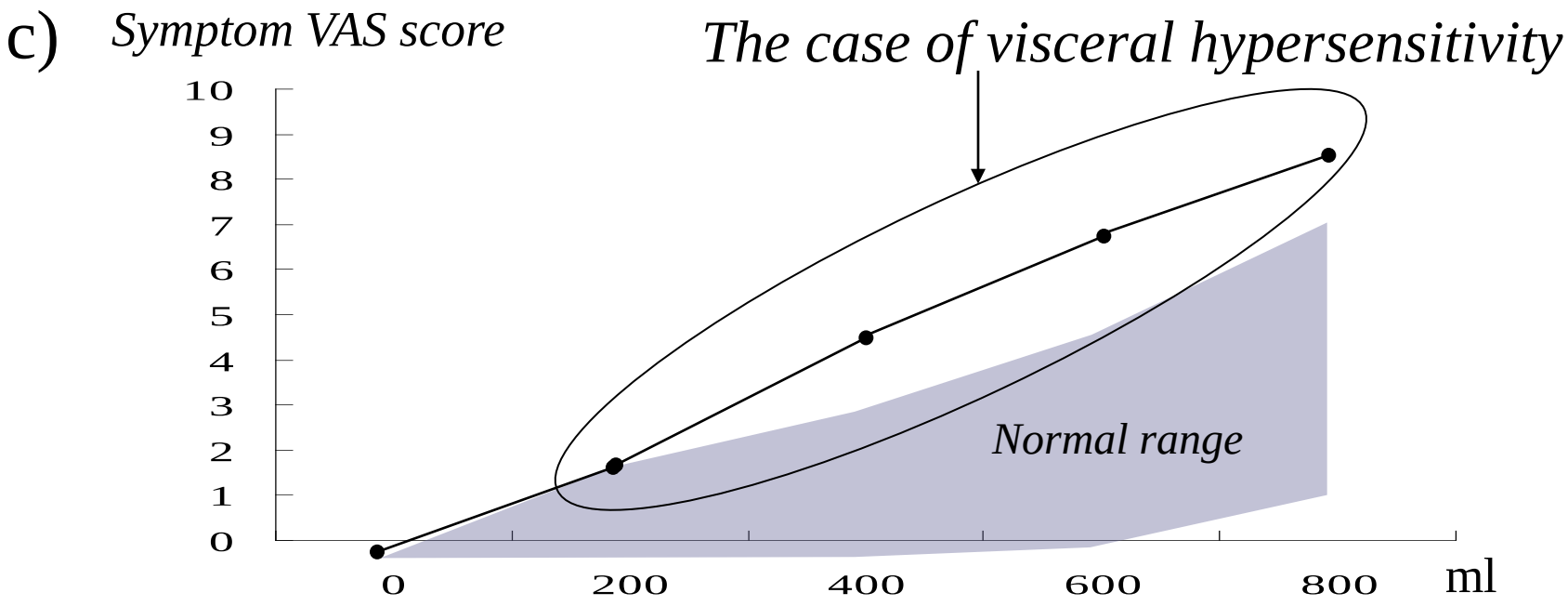
c)
Symptom VAS score
The case of visceral hypersensitivity
10
9
8
7
6
5
4
3
2
1
0
Normal range
0
200
400
600
800
ml

Figure 1

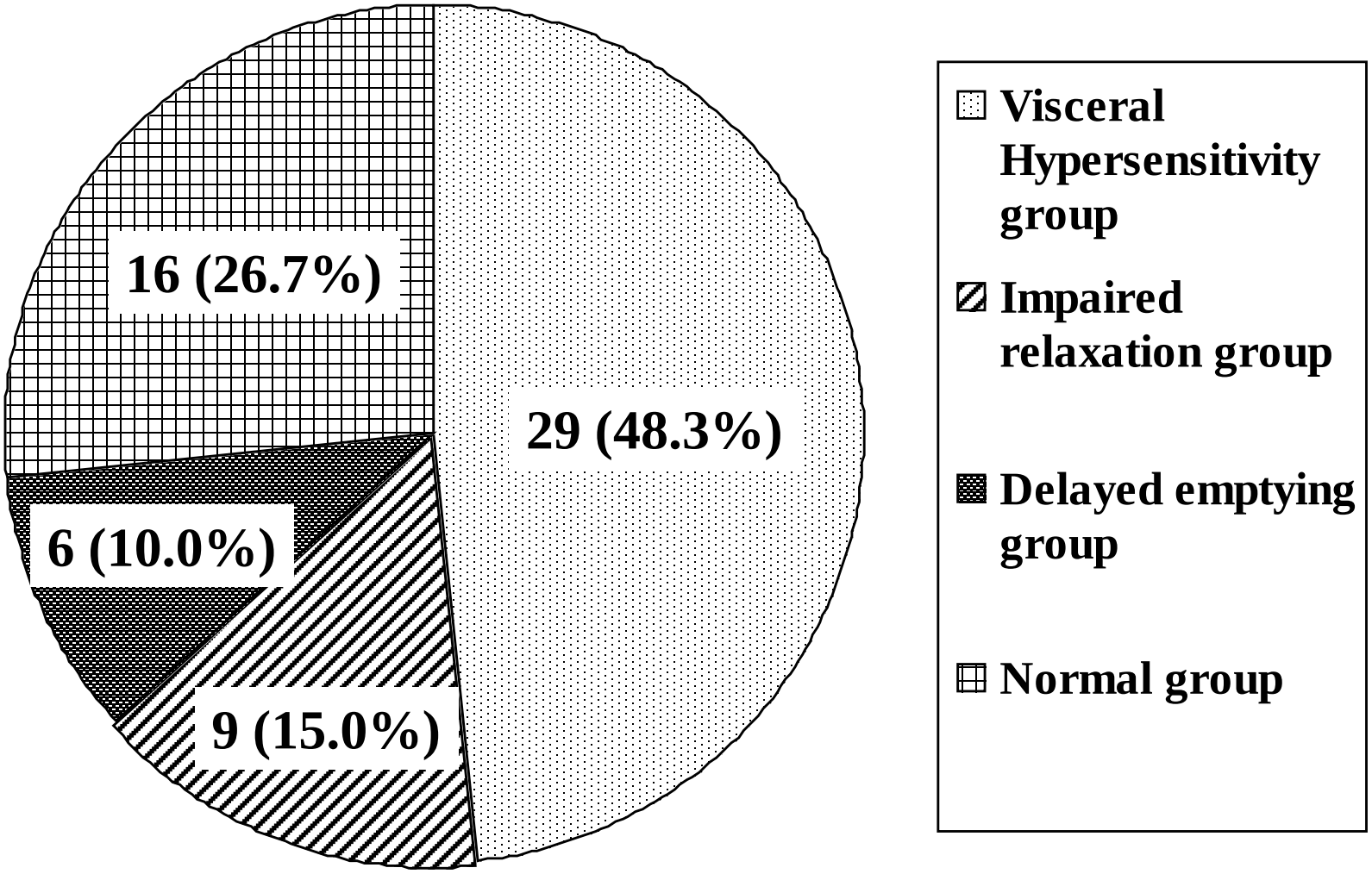
16 (26.7%)
29 (48.3%)
6 (10.0%)
9 (15.0%)
Visceral Hypersensitivity group
Impaired relaxation group
Delayed emptying group
Normal group

Figure 2