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Evaluation of Duodenal Hypersensitivity to Acid Using Transnasal Endoscopy

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1. Introduction

According to the Rome III classification, functional gastroduodenal disorders (FGIDs) in adults are subdivided into six domains. Functional dyspepsia (FD) is a subcategory of the FGIDs. It is characterized by the presence of symptoms that are believed to be associated with gastroduodenal lesions, particularly epigastric pain or burning, postprandial fullness, or early satiation, without the evidence of organic disease to explain the onset of these symptoms at least 6 months before diagnosis (Tach J et al., 2006). Furthermore, FD is divided into 2 subtypes postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS). The diagnostic criteria for PDS include the presence of 1 or both of the following symptoms several times in a week: bothersome postprandial fullness occurring after ordinary-sized meals, and early satiation that prevents finishing a regular meal. The diagnostic criteria for EPS include the presence of all of the following symptoms: moderately severe pain or burning localized to the epigastrium at least once per week, and intermittent pain, not generalized or localized to other abdominal or chest regions, not relieved by defecation or passage of flatus, and not fulfilling the criteria for gallbladder and sphincter of Oddi disorders.

FD is a functional disorder that affects 10-30% of the population worldwide. The results of an Itarian population-based study, indicated that the prevalence rates of FD were 11%. Of these, PDS, EPS, and PDS accompanied with EPS were 67.5%, 48.2%, and 15.8% respectively (Zagari RM et al.,2010).The results of a Swedish population-based study, indicated that the prevalence rates of FD, PDS, EPS, and PDS accompanied with EPS were 15.7%, 12.2%, 5.5%, and 1.7%, respectively (Aro P et al., 2009). The results of a Norwegian population-based study, showed that the lifetime prevalence rate of FD was 23% in men and 18% in women (Johnsen et al., 1988), and that in the United States, was 29% (Shaib Y et al., 2004).

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2. Pathogenesis and evaluation

Different factors such as delayed gastric emptying (Stanghellini V et al., 1996; Sarnelli G et al., 2003), hypersensitivity to gastric distension (Bradette M et al., 1991; Mearin F et al., 1991; Barbera R et al., 1995; Tack J et al., 2001), impaired gastric accommodation to a meal (Tach J et al., 1998), abnormal duodenojejunal motility (Holtmann G et al., 1996; Wilmer A et al., 1998), duodenal motor and sensory dysfunction (Samsom M et al., 1999; Schwarz MP et al., 2001), duodenal hypersensitivity (Schwartz MP et al., 2001), *Helicobacter pylori* infection, and psychosocial factors have been implicated in the pathogenesis of FD. Among these factors, acid is thought to be more important because proton pump inhibitors (PPIs) and histamine 2 (H2)-receptor antagonists have been proposed to be effective therapies for a subset of patients with FD.

2.1 Duodenal hypersensitivity to acid in patients with FD

Lee *et al.* (2004) reported that acid infusion into the duodenal bulb induced dyspepsia in healthy volunteers, and the symptoms of dyspepsia are more readily observed in patients with FD than in healthy subjects (Samsom *et al.*, 1999). Increased duodenal acid exposure plays a role in the onset of dyspeptic symptoms in patients with FD having prominent nausea (Lee *et al.*, 2004). A recent study indicated that acid infusion into the stomach predominantly induced dysmotility-like dyspeptic symptoms in healthy Japanese control subjects (Miwa *et al.*, 2007). PPIs and H2-receptor antagonists have been proposed as effective therapies for treating FD (Delaney *et al.*, 2005; Veldhuyzen van Zanten *et al.*, 2005; Kinoshita *et al.*, 2005; Seno *et al.* 2005). Guidelines for the management of dyspepsia suggest that PPI therapy is more effective than a placebo or H2-receptor antagonists in relieving the symptoms of patients with uninvestigated dyspepsia (Talley *et al.*, 2005).

2.2 Duodenal acid and gastroduodenal motility

Duodenal acidification suppresses antral contractions. Matsunaga *et al.* (1994) reported that intragastric acidification and intraduodenal acidification at pH 1.0 inhibited spontaneous phase III activity in dogs. Simrén *et al.* (2003) reported that after acid infusion in healthy volunteers, antral contractions were lesser and the number of contractions in the proximal duodenum was greater than those before the infusion. It has been shown that the greater the concentration of acid in the duodenum, the greater is the inhibition of gastric emptying (Hunt *et al.*, 1972). Duodenal pH influences interdigestive gastric motility in humans. Lowering of the duodenal pH prevents the occurrence of the gastric phase III (Woodtli *et al.*, 1995), and, in animals, duodenal acidification induces gastric relaxation by exerting an inhibitory effect on the stomach (Lu *et al.*, 1999). Duodenal acidification has an inhibitory effect on gastric emptying (Danzer *et al.*, 2004; Raybould *et al.*, 1993; Cooke, 1974; Mearadji *et al.*, 1999; Parkman *et al.*, 1998), and hydrochloric acid (HCl) may restrict gastric outflow by inducing tonic occlusion of the duodenum (Parkman *et al.*, 1998).

2.3 Pathophysiological mechanism of acid-sensing system

Visceral organs receive dual innervation from primary afferents commonly referred to as sympathetic afferents (splanchnic nerves) and parasympathetic afferents (vagus nerves). Lamb *et al.* (2003) reported that electromyographically recorded visceromotor responses increased after HCl administration in rats, but vagotomy and pretreatment with capsaicin abolished these responses. Their findings indicated that vagal pathways are involved in

mediating signals for the noxious stimulation of the stomach. Further, Scicho *et al.* (2005) reported that gastric acidification increased the expression of phosphorylated extracellular signal-regulated kinase-1 and -2 (p-ERK1/2) in the dorsal root ganglion neurons via *N*-methyl-D-aspartate receptors. They suggested that sympathetic pathways are involved in mediating signals for noxious stimulation of the stomach. Noxious mechanical stimulation showed that most of the increased p-ERK1/2 neurons coexpressed transient receptor potential vanilloid receptor 1 and acid-sensing ion channel 3 (Sakurai *et al.*, 2008).
Transient receptor potential vanilloid receptor 1 and the acid-sensing ion channel 3 are largely involved in the acid-induced nociception in mammals (Ugawa *et al.*, 2002), but it is still unknown which receptors of the peripheral sensory pathways encode and integrate an acidinduced nociceptive event in the gastric mucosa and the duodenal mucosa. Akiba *et al.* (2002) reported that the capsaicin pathway is an acid-sensing pathway that promotes hyperemia and mucus secretion in response to luminal acid in the duodenum.

2.4 Method for evaluating duodenal hypersensitivity to acid and gastric motility

Duodenal hypersensitivity to acid is one of the more important factors in the pathogenesis of FD. Although manometric methods, scintigraphic methods, electrogastrography and ultrasonography have been used to evaluate enterokinesis, a practical method for evaluating duodenal hypersensitivity to acid has not been reported. Transnasal endoscopy is a rescently developed, non-invasive and nondiscomforting method for examination of the upper gastrointestinal tract (Yagi *et al.*, 2005; Murata *et al.*, 2007). We developed a new method for evaluating duodenal hypersensitivity to acid and gastric motility by duodenal acidification using transnasal endoscopy (Ishii *et al.*, 2008).

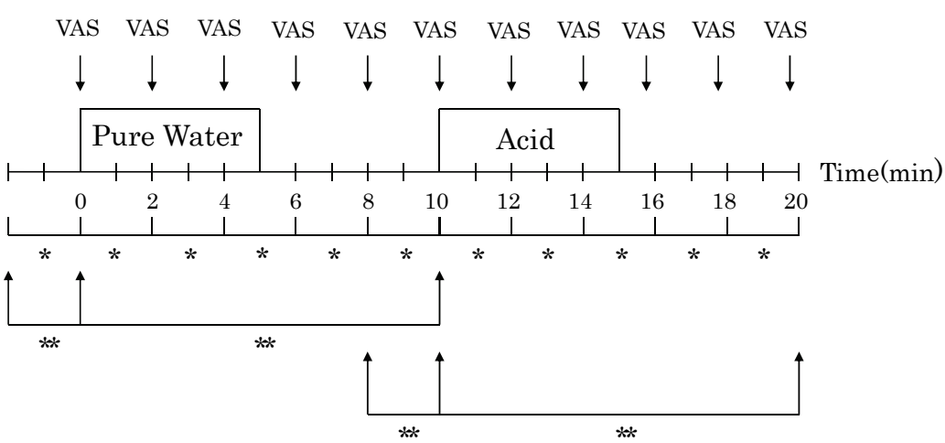

Fig. 1. *Number of antral contractions every two minutes; **Motility number; VAS: Visual Analogue Scale

The study protocol is shown in Fig. 1. All subjects underwent transnasal endoscopy as required in the left lateral decubitus position in the morning after overnight fasting. The infusion of air into their stomachs was minimized in order to observe their gastric motility. An infusion tube (outer diameter 1.5 mm) was then introduced by transnasal endoscopy until the tip was located in the duodenal bulb. The subjects changed their body position to the supine position, and their antral contractions and dyspeptic symptoms were evaluated before and after a duodenal infusion of pure water (36.5°C, 100 ml) and acid (36.5°C, 0.1 N

HCl, 100 ml). The images of transnasal endoscopy were recorded from the beginning until the end on a DVD and were analyzed after finishing the examination. We infused 100 ml of pure water and acid at a rate of 20 ml/min. The use of an electronic infusion pump, ensured

	2 min	4 min	6 min
Heavy feeling in the stomach			
Nausea or feeling sick			
Bloating			
Belching			
Cramping pain in the stomach			
Dull pain in the stomach			
Pricking pain in the stomach			
Tickling or tingling in the throat			
Sour or bitter taste			
Feeling that something is stuck in the throat			
Burning sensation in the chest			

Fig. 2.

Symptoms	Maximum severity scale (cm) (Mean±SEM)		
	0.1mol/L HCl	Pure Water	P-value
Heavy feeling in the stomach	4.76±0.74	0.54±0.24	0.0001
Nausea or feeling sick	4.65±1.1	0.19±0.16	0.001
Bloating	3.66±0.8	0.54±0.24	0.0006
Belching	1.61±0.61	0.76±1.1	0.2349
Cramping pain in the stomach	3.39±0.88	1.0±0.45	0.0016
Dull pain in the stomach	4.05±0.83	0.49±0.23	0.0005
Pricking pain in the stomach	1.58±0.72	0.51±0.75	0.125
Tickling or tingling in the throat	2.35±0.91	0.42±0.17	0.0539
Sour or bitter taste	1.1±0.16	0.55±0.09	0.0982
Feeling that something is stuck in the throat	1.6±0.64	0.45±0.25	0.0932
Burning sensation in the chest	2.67±0.75	0.16±0.1	0.0033

Maximum severity on the 10 cm visual analogue scale after infusion of 0.1 mol/L hydrochloric acid (HCl) or pure water (n=14)

Table 1.

that the subjects were blinded to the nature (acid or pure water) of the infusion. The acid infusion was started 5 min after the infusion of pure water was finished. The severity of each symptom was assessed by each subject using a 10-cm visual analogue scale every 2 min (Fig. 2). The symptoms assessed were as follows: a heavy feeling in the stomach, bloating, nausea or feeling sick, belching, a dull pain in the stomach, cramping pain in the stomach, a pricking pain in the stomach, tickling or tingling sensation in the throat, a sour or bitter taste, a feeling that something is stuck in the throat, and a burning sensation in the chest. The symptom severity scales were set at 0 cm before the duodenal infusion of water and acid. The maximum severity scale was calculated as the mean of the individual maximum values. We evaluated the differences between the maximum severity scales in the infusion of pure water and acid. Antral contractions beginning every 2 min before the duodenal infusion of water were counted every 2 min until the end of the examination. The macroscopic waves of gastric peristalsis propagating from the gastric body to the antrum were counted. The motility number was defined as the mean number of antral contractions in 1 min. We evaluated the differences between the motility numbers before and after the infusion of pure water and those before and after acid infusion. We compared the changes in the symptom severity scales, the maximum severity scales of each subject, the number of antral contractions, and the motility number between the acid and pure water infusion. Using this method, we showed that the maximum severity scale of a heavy feeling in the stomach, and other symptoms was significantly greater after the acid infusion than that the pure water infusion in healthy volunteers (Table 1). During pure water infusion, no changes were observed between the motility numbers. On the other hand, the motility number significantly decreased after duodenal acidification (before *vs.* after: 2.93 ± 0.12 times *vs.* 1.11 ± 0.23 times, $P<0.0001$) (Fig. 3).

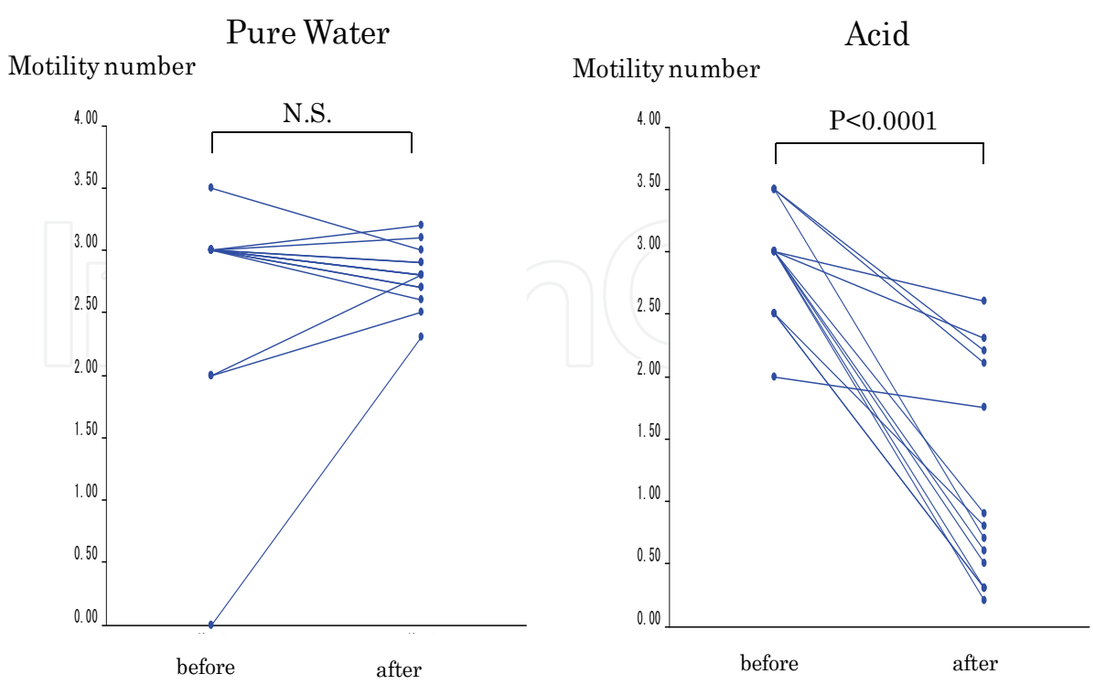

Fig. 3.

Furthermore, using this method we evaluated duodenal hypersensitivity to acid in healthy volunteers and patients with FD (Ishii *et al.*, 2010). The study protocol is shown in Fig. 4. In this study, we infused the patients with 20 ml of HCl at a rate of 20 ml/min. The severity of 12 symptoms was assessed by each subject using a 100-mm visual analogue scale (VAS) from the time acid infusion was started up to 30 min after the initiation of the infusion.

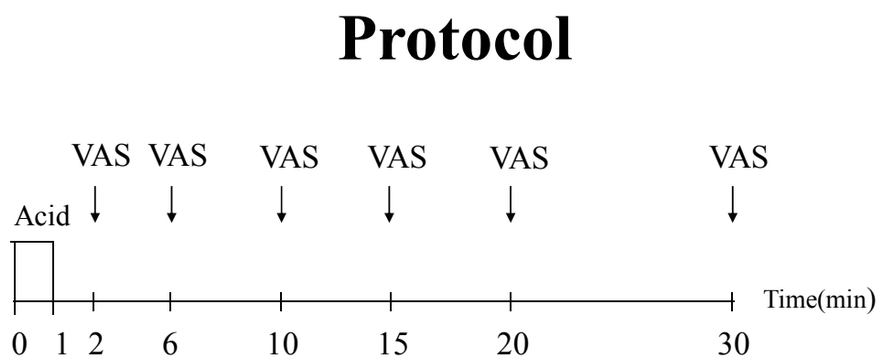

Fig. 4. Study protocols. This study consisted of monitoring of the assessment of symptoms using VAS

Symptoms	Maximum severity scale (mm) (Mean±SEM)		
	Patients with FD	Healthy volunteers	P-value
Heavy feeling in the stomach	25.5±4.4	5.9±2.0	<0.001 *
Nausea or feeling sick	14.4±4.3	4.4±1.9	0.036 *
Bloating	39.1±5.1	14±3.5	<0.001 *
Belching	20.0±4.9	9.6±6.3	0.254
Cramping pain in the stomach	19.4±5.0	5.4±2.7	0.017 *
Dull pain in the stomach	21.8±5.0	4.5±2.3	0.003 *
Prickling pain in the stomach	12.9±4.1	4.8±2.2	0.084
Tickling or tingling in the throat	9.7±3.2	0.6±0.6	0.008 *
Sour or bitter taste	8.9±3.1	0.6±0.6	0.011 *
Feeling that something is stuck in the throat	18.6±4.3	1.9±1.1	<0.001 *
Burning sensation in the chest	10.6±3.6	3.1±2.0	0.073
Early satiety	35.6±5.3	9.0±3.9	<0.001 *

Maximum severity on the 100-mm visual analogue scale after infusion of 0.1 mol/L hydrochloric acid (HCl) between healthy volunteers and patients with FD.
*P < 0.05, 2-sided non-paired *t* test

Table 2. Maximum severity scales between healthy volunteers and patients with FD

The maximum severity scale was defined as the maximum score of the symptom severity scale. The VAS was set at 0 mm just before the duodenal infusion of acid. The total score was defined as the aggregate score of the maximum severity scale for the 12 symptoms.

The differences in the rate of incidence of dyspeptic symptoms, maximum severity scales, and total scores between patients with FD and healthy volunteers were evaluated.
The rates of dyspeptic symptoms in patients with FD and healthy volunteers after acid infusion were 88.6% and 75%, respectively (P = not significant, using the X^2-test). The maximum severity scales of a heavy feeling in the stomach, nausea or feeling sick, bloating, cramping pain in the stomach, dull pain in the stomach, tickling or tingling in the throat, sour or bitter taste, feeling that something is stuck in the throat and early satiety significantly increased after acid infusion in patients with FD than in healthy volunteers ($P < 0.05$, using the two-sided non-paired t-test) (Table 2). There were significant differences in the total scores (patients with FD *vs* healthy volunteers: 233.8 ± 37.8 *vs* 63.9 ± 14.6; $P < 0.001$, using the two-sided nonpaired t-test) (Fig. 5). We found that duodenal acidification induced dyspeptic symptoms more significantly in patients with FD than in healthy volunteers.

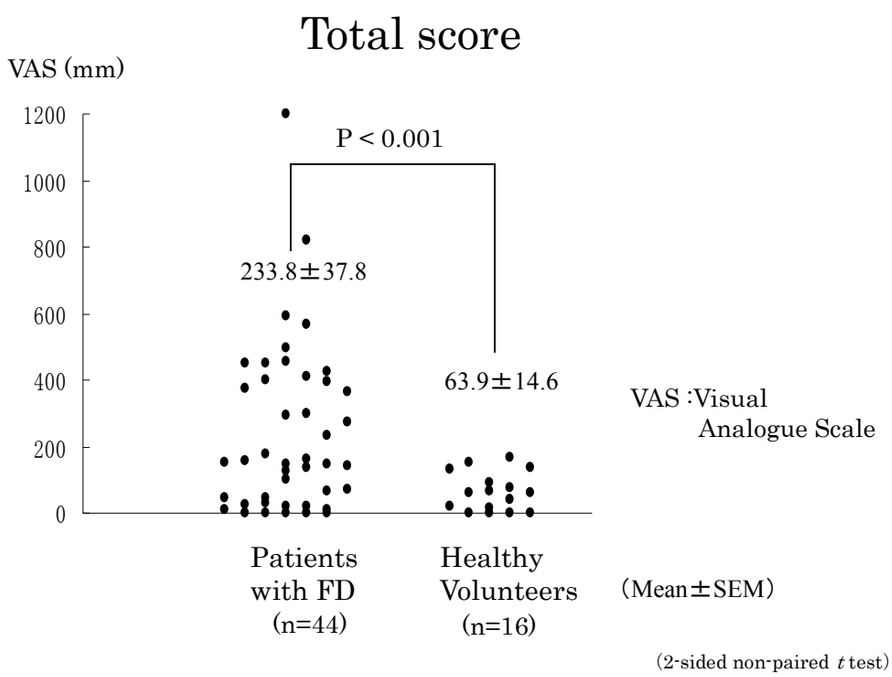

Fig. 5.

3. Conclusion

The effects of duodenal acidification by transnasal endoscopy significantly increased various dyspeptic symptoms not suppresses this symptoms. Further, this method enabled the evaluation of duodenal hypersensitivity to acid in healthy volunteers and in patients with FD. Using this method, we might be able to clarify a correlation between duodenal hypersensitivity to acid and the effectiveness of PPI therapy for the treatment of FD. A further examination is needed.

4. Acknowledgment

We thank nurses and officers at the Kawasaki Medical School for their kind help with the present survey.

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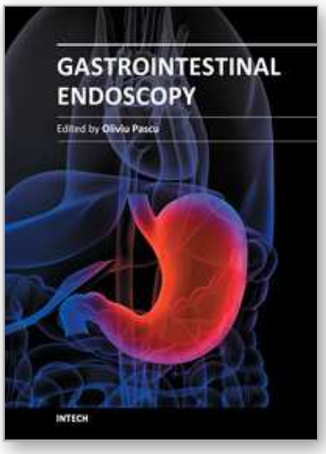

Gastrointestinal Endoscopy

Edited by Prof. Oliviu Pascu

ISBN 978-953-307-385-9

Hard cover, 272 pages

Publisher InTech

Published online 19, July, 2011

Published in print edition July, 2011

Endoscopy has had a major impact in the development of modern gastroenterology. By using different data it provided a better understanding of pathogenic mechanisms, described new entities and changed diagnostic and therapeutic strategies. Meanwhile, taking advantage of many technical advances, endoscopy has had a developed spectacularly. Video-endoscopes, magnification, confocal and narrow-band imaging endoscopes, endoscopic ultrasounds and enteroscopes emerged. Moreover, endoscopy has surpassed its function as an examination tool and it became a rapid and efficient therapeutic tool of low invasiveness. InTech Open Access Publisher selected several known names from all continents and countries with different levels of development. Multiple specific points of view, with respect to different origins of the authors were presented together with various topics regarding diagnostic or therapeutic endoscopy. This book represents a valuable tool for formation and continuous medical education in endoscopy considering the performances or technical possibilities in different parts of the world.

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