Esophagus (2017) 14:221–228
DOI 10.1007/s10388-017-0575-7

REVIEW ARTICLE

Mechanisms underlying excessive esophageal acid exposure in patients with gastroesophageal reflux disease

Katsuhiko Iwakiri[1] · Shintaro Hoshino[1] · Noriyuki Kawami[1]

Received: 3 March 2017 / Accepted: 19 April 2017 / Published online: 25 April 2017

Abstract The cause of reflux esophagitis (RE) is excessive esophageal acid exposure. Acid reflux and acid clearance after acid reflux are important factors related to excessive esophageal acid exposure. The main mechanism responsible for acid reflux is transient lower esophageal sphincter relaxation (TLESR), which is LES relaxation not associated with swallowing, and acid reflux caused by low LES pressure is rare. The frequency of TLESR in the postprandial period does not significantly differ between healthy subjects and gastroesophageal reflux disease (GERD) patients; however, the proportion of acid reflux episodes during TLESR is significantly higher in GERD patients. The layer of acid that appears above the dietary layer immediately below the esophagogastric junction (acid pocket) is attracting increasing attention as a cause of the difference in the proportion of acid reflux episodes during TLESR. The proportion of acid reflux episodes during TLESR is significantly higher when the acid pocket is present in the hernia sac than when it is located below the diaphragm. The acid pocket also shows upward migration and reaches the esophageal side of the esophagogastric junction, and the acid pocket itself has been suggested to cause mucosal damage in the lower esophagus. The amplitude and success rate of primary peristalsis decreases with increases in the severity of RE, leading to excessive esophageal acid exposure. Furthermore, the success rate of secondary peristalsis is lower in GERD patients than in healthy subjects.

✉ Katsuhiko Iwakiri
k-iwa@nms.ac.jp

[1] Department of Gastroenterology, Nippon Medical School, Graduate School of Medicine, 1-1-5 Sendagi, Bunkyo-ku, Tokyo 113-8603, Japan

Keywords GERD · Reflux esophagitis · Excessive esophageal acid exposure · Transient LES relaxation · Primary peristalsis · Hiatal hernia

Introduction

In Japan, the number of patients with gastroesophageal reflux disease (GERD) has been rapidly increasing since 1990, and approximately 10% of patients who undergo endoscopic examinations have reflux esophagitis [1]. While GERD including reflux esophagitis is a benign disease, the problem is what the quality of life in patients with GERD is impaired. An increase in GERD patients not infected by *Helicobacter pylori*, a Westernized diet, and obesity has been suggested as factors that have increased the prevalence of reflux esophagitis. The severity of reflux esophagitis is mild, i.e., grade A or B by the LA classification, in approximately 90% of patients, and endoscopic healing of more than 90% is achieved with a standard dose of PPI [1]; however, an increase in severe reflux esophagitis not healed by standard-dose PPI therapy has recently been reported in Japan [2]. The cause of esophageal mucosa breaks in reflux esophagitis is excessive esophageal acid exposure, which significantly increases in severe reflex esophagitis [3]. This review summarizes excessive esophageal acid exposure as a cause of reflux esophagitis.

Esophageal motility after swallowing in healthy subjects

The lower esophageal sphincter (LES) relaxes after swallowing to clear solid and liquid contents from the esophagus and then contracts at an LES pressure of 15–20 mmHg

to prevent reflux from the stomach into the esophagus [4]. LES relaxation starts after swallowing and primary peristalsis appears in the upper esophagus, and ends when primary peristalsis reaches the LES [4]. The duration of LES relaxation associated with swallowing is 5–8 s [5]. Since gastric pressure is approximately 5 mmHg higher and esophageal pressure is approximately 5 mmHg lower than atmospheric pressure during inspiration, a pressure gradient of approximately 10 mmHg exists between the stomach and esophagus [6]. Therefore, acid reflux may occur if LES pressure is very low. Besides swallowing, LES relaxation occurs via esophagus-distending stimuli (liquid or air reflux and food residue in the esophagus).

Mechanisms underlying excessive esophageal acid exposure in reflux esophagitis patients

Reflux esophagitis is caused by excessive esophageal acid exposure [3], and factors related to excessive esophageal acid exposure include acid reflux, the esophageal bolus clearance of acid, and esophageal hiatal hernia.

Acid reflux

The continuous measurement of LES pressure revealed that acid reflux occurs when LES pressure is markedly reduced. Conditions with markedly reduced LES pressure are caused by (a) relaxation of the LES (LES pressure is nearly zero) or (b) intrinsically very low LES pressure.

Acid reflux during LES relaxation

(a.1) LES relaxation not associated with swallowing (transient LES relaxation)

More than 95% of acid reflux occurring during LES relaxation is not accompanied by swallowing. LES relaxation unrelated to swallowing is called transient LES relaxation (TLESR) [7] (Fig. 1). TLESR is also the physiological mechanism responsible for belching and is not a pathological phenomenon. TLESR is commonly accompanied by air reflux, and sometimes by acid reflux. Between 80 and 100% of acid reflux episodes in healthy subjects and 56–73% in GERD patients are caused by TLESR, which is one of the main mechanisms responsible for acid reflux in healthy subjects and GERD patients [8–13]. Although the mechanisms underlying acid reflux in patients with endoscopically demonstrated non-erosive reflux disease (NERD) have not yet been elucidated in detail, we previously demonstrated that all acid reflux episodes were caused by TLESR in NERD patients [14]. TLESR is defined as (i) no swallowing during the 4 s before or 2 s after the beginning of LES relaxation, (ii) a residual pressure during LES relaxation of <2 mmHg, (iii) an LES relaxation rate of ≥1 mmHg/s, and (iv) an LES relaxation time of ≥10 s [7]. While the duration of LES

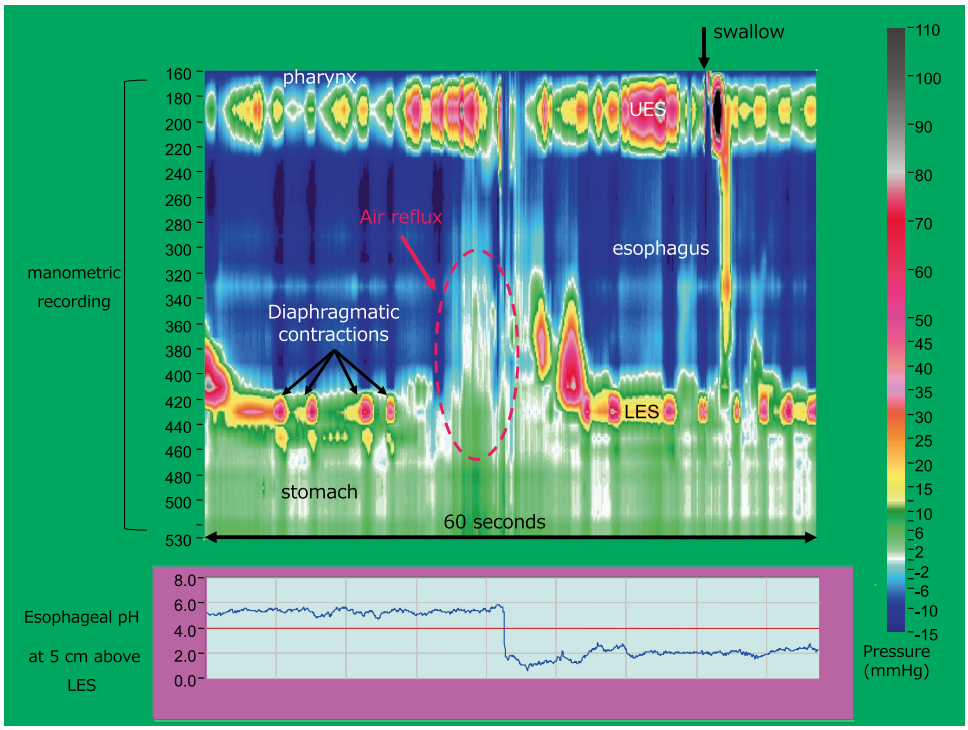

Fig. 1 High-resolution manometric and esophageal pH recordings at 5 cm above the LES. There is no pharyngeal swallow signal from 4 s before to 2 s after the onset of LES relaxation; therefore, this is transient LES relaxation. During transient LES relaxation, regular increases are not observed in diaphragmatic hiatal pressure due to diaphragmatic contractions during inspiration, and acid reflux is detected approximately 10 s after the beginning of LES relaxation. *LES* lower esophageal sphincter, *UES* upper esophageal sphincter

relaxation associated with swallowing is 5–8 s, the average duration of TLESR is approximately 15–20 s, with a maximum of approximately 30 s [7]. Furthermore, while the crural diaphragm is not inhibited during LES relaxation with swallowing, it is suppressed during TLESR [15]. In addition, intense contractions of the LES and primary or secondary peristalsis are often observed at the end of TLESR.

a.1.1 Frequency of TLESR and proportion of acid reflux episodes during TLESR.

Since the frequency of TLESR was reported to be significantly higher in GERD patients than in healthy subjects by Dodds et al. [9], GERD may be associated with a high frequency of TLESR. The study by Dodds et al. [9] was performed using subjects in the recumbent position; however, acid reflux often occurs postprandially in the vertical position. An evaluation of the frequency of TLESR in the vertical position revealed no significant differences between healthy subjects and reflux esophagitis patients [13, 16–19]. These findings indicate that the frequency of TRESR is unrelated to excessive esophageal acid exposure.

Although TLESR is not necessarily accompanied by acid reflux, the proportion of acid reflux episodes during TLESR at 5 cm above the LES was found to be higher in reflux esophagitis patients than in healthy subjects [7, 9–13, 16, 17]. Based on these findings, excessive esophageal acid exposure is considered to be caused by a high proportion of acid reflux episodes during TLESR rather than a high frequency of TLESR. The higher proportion of acid reflux episodes during TLESR in reflux esophagitis patients may be explained by differences in the volume of acid reflux and the gastroesophageal pressure gradient; however, this needs to be clarified in more detail.

As for differences between Japan and Western countries, the proportion of acid reflux episodes during TLESR was previously reported to be higher in reflux esophagitis patients than in healthy subjects in Japan and Western countries, but was lower in reflux esophagitis patients and healthy subjects in Japan than in Western countries [16]. These findings may explain the lower prevalence of severe reflux esophagitis in Japan than in Western countries.

a.1.2 Factors that affect the frequency of TLESR.

Gastric distension by a balloon [20], gas [21], or food [22, 23] is a factor that increases the frequency of TLESR. An increase in intra-abdominal gastric pressure by obesity also increases the frequency of TLESR [24]. The site of the reception of these gastric distension stimuli is considered to be near the cardia [25]. Although many patients develop heartburn after the intake of a high-fat meal, there is currently no consensus on the relationship between a high-fat diet and gastric acid reflux [26–29]. Regarding the relationship between fat intake and TLESR, no significant differences were reported in the frequency of TLESR [28, 29], whereas acid reflux occurred more frequently during TLESR after the ingestion of a high-fat meal [28]. As for other food items, beer, coffee, chocolate, and onions have been reported to increase esophageal acid exposure; however, their relationships with the frequency of TLESR currently remain unclear. On the other hand, the recumbent position [22, 30], sleep [31, 32], and anesthesia [33] have been identified as factors that suppress the frequency of TLESR.

a.1.3 Neural reflex arcs of TLESR.

Since the frequency of TLESR is reduced by suppressing excitation of the vagal reflex, TLESR is considered to be mediated by the vagus nerve [34]. Furthermore, splanchnic nerve section has no effect on the frequency of TLESR; therefore, the splanchnic nerve is not considered to be involved in TLESR [35]. The reflex arc of TLESR begins with the afferent fibers of the vagus nerve, which are distributed in the gastric muscle layer and sense gastric distension. This signal of gastric distension is sent to the solitary nucleus of the brainstem via the afferent fibers of the vagus nerve and transferred to the dorsal motor nucleus of the vagus nerve from the pattern generator, which controls the frequency of TLESR. This signal is considered to be sent to the intramural plexuses of the LES via the efferent fibers of the vagus nerve and induce TLESR (Fig. 2) [36–43]. As previously reported, neurotransmitters and their receptors are located in afferent fibers of the vagus nerve, arc nucleus, and dorsal motor nucleus of the vagus nerve. Acetylcholine, cholecystokinin (CCK), gamma amino butyric acid (GABA), glutamic acid, nitric oxide (NO), and opiates may be involved in transient LES relaxation in animals and humans [6]. Acetylcholine,

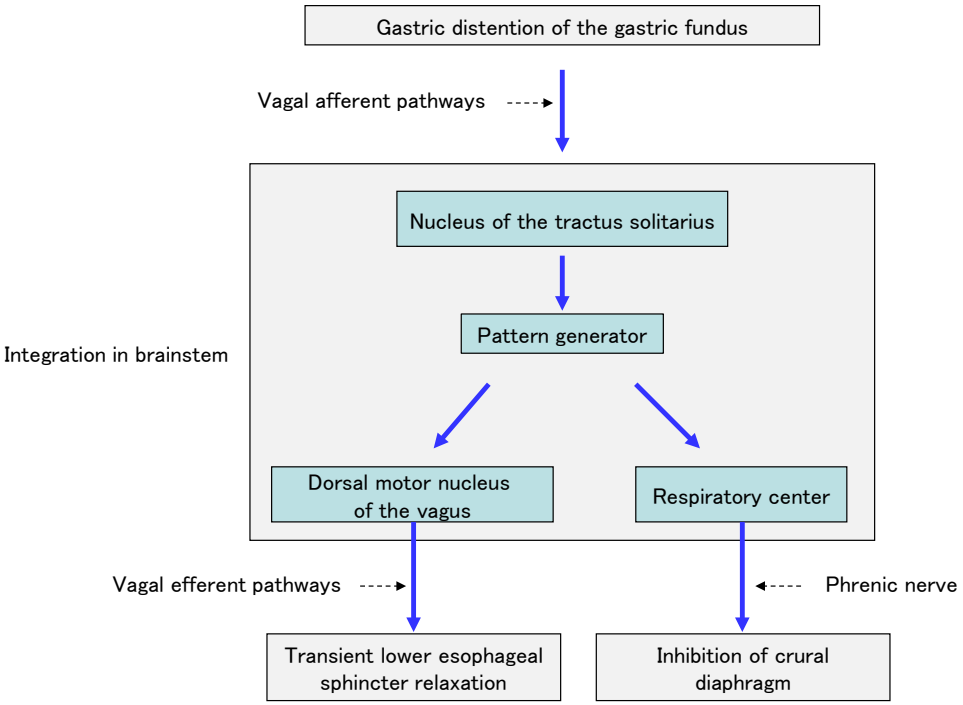

Fig. 2 Triggering and control of transient lower esophageal sphincter relaxation

NO, GABA-B, 5-hydroxytryptamine ($5HT_3$), opiates, and CCK receptors are located in the vagus nerve nucleus within the brainstem and its surroundings, whereas CCK, $5HT_3$, and GABA-B receptors are in the afferent vagus nerve [40]. The crural diaphragm is inhibited during TLESR, presumably via the afferent vagus nerve, which mediates TLESR [44]. While afferent fibers are considered to suppress the nuclei of the respiratory centers, further studies are needed to obtain more detailed information.

a.2 Acid reflux during LES relaxation associated with swallowing.

Acid reflux during LES relaxation associated with swallowing accounts for less than 5% of acid reflux during LES relaxation and is a rare mechanism of acid reflux. Acid reflux occurring after swallowing is often observed when primary peristalsis is defective or incomplete [10, 45]. On the other hand, acid reflux is rarely observed when normal primary peristalsis occurs after swallowing. The rareness of acid reflux during LES relaxation after swallowing is ascribed to (i) the shorter duration of LES relaxation (5–8 s) than TLESR, (ii) the absence of crural diaphragm inhibition, unlike TLESR, and (iii) occlusion of the esophageal lumen due to the appearance of primary peristalsis after swallowing.

Acid reflux associated with low LES pressure

Acid reflux due to low LES pressure occurs when intrinsic LES pressure is extremely low. Free reflux and strain reflux are the mechanisms responsible for acid reflux in this state. Free reflux occurs when LES pressure is nearly zero (<2 mmHg). Strain reflux is induced by a rapid increase in abdominal pressure when LES pressure is low (commonly <5 mmHg). These mechanisms of acid reflux are observed in patients with low LES pressure and are mostly responsible for severe reflux esophagitis. Acid reflux due to low LES pressure is observed in 15–45% of patients with severe reflux esophagitis [16, 17, 46], but rarely in healthy subjects, NERD patients, and patients with mild reflux esophagitis [14, 46].

Esophageal bolus clearance of acid

The delayed esophageal bolus clearance of acid may cause excessive esophageal acid exposure. Esophageal peristalsis plays a key role in the clearance of refluxed acid from the esophagus. The esophageal bolus clearance of acid is a two-step process of bolus clearance and acid neutralization [47, 48]. If a 15-ml or smaller bolus of acid is instilled into the esophagus, most of the acid may be cleared from

the esophagus by peristaltic contractions; the remainder of the acid lining the esophagus mucosa is neutralized by saliva traversing the esophagus during subsequent swallow-induced peristaltic contractions. Seven to ten swallows following esophageal acidification are needed to restore esophageal pH to normal—between 5 and 7. Hypotensive and failed peristalsis are ineffective at clearing acid from the esophagus [49, 50].

The factors that constitute peristaltic waves are the amplitude of esophageal contractions and frequency of normal peristalsis, and are significantly lower in patients with severe reflux esophagitis (grades C and D by the LA classification) than in healthy subjects and patients with mild reflux esophagitis, resulting in the delayed esophageal bolus clearance of acid [51, 52]. This delay in acid clearance is one of the causes of excessive esophageal acid exposure observed in patients with reflux esophagitis. While no significant difference has been reported in primary peristalsis between patients with mild reflux esophagitis and healthy subjects, an evaluation by the classification of mild reflux esophagitis into grades A and B revealed a significant decrease in the amplitude of primary peristalsis in the lower esophagus in patients with grade B than grade A reflux esophagitis [52]. However, a recent study showed that the propagation of contraction waves in the entire esophagus with a pressure of 20 mmHg or higher was necessary for esophageal clearance [53]; therefore, differences in the amplitude of contraction waves between grades A and B are not considered to be clinically significant.

Secondary peristalsis is also important for the esophageal bolus clearance of acid. Secondary peristalsis is characterized by peristaltic waves induced by the esophageal distention (liquid reflux and air reflux) and is important for refluxed liquid and food clearance in the esophagus not cleared by primary peristalsis. Since swallowing frequently occurs during the daytime, defective secondary peristalsis is not a major issue. However, salivary secretion is suppressed during the nighttime and primary peristalsis does not occur; therefore, secondary peristalsis is important for the esophageal bolus clearance of acid in nighttime reflux. The frequency of secondary peristalsis has been reported to be significantly lower in GERD and NERD patients than in healthy subjects [54, 55].

Esophageal hiatal hernia

Regarding the relationship between TLESR and esophageal hiatal hernia, the frequency of TLESR was previously reported to be significantly higher in the condition of the continuous infusion of a small amount of air into the stomachs of patients with than in those without hiatal hernias [56]. However, 24-h esophageal manometry and pH monitoring under physiological conditions revealed that the number of acid reflux episodes during TLESR did not significantly differ according to the presence or absence of a hiatal hernia, whereas acid reflux during LES relaxation after swallowing and that associated with low LES pressure were significantly greater in patients with than in those without hiatal hernias [57].

The layer of acid that appears postprandially above the dietary layer immediately below the esophagogastric junction (EGJ) has been identified as a source of postprandial acid reflux [58]. This layer of acid immediately below the EGJ is called the “acid pocket” [59]. The acid pocket migrates upward, reaches the esophageal side of the EGJ, and may cause mucosal damage to the lower esophagus [60–62]. This upward migration of the acid pocket, sometimes referred to as an “acid film”, is more likely to occur in GERD patients, particularly in the supine position [61]. The length of the acid pocket has been reported to be long in GERD patients [60], and its location is of particular importance [62]. When the acid pocket is located in the hernia sac (supradiaphragmatic location), the proportion of acid reflux episodes during TLESR (70–85%) is significantly higher than when it is located below the diaphragm (7–20%) [62].

In healthy subjects, acid reflux mostly occurs when the acid pocket is present in the hernia [63]. Although hiatal hernias are often absent in healthy subjects, a previous study that evaluated the postprandial location of the EGJ showed that it was elevated by 4.3 cm (median) during TLESR. Therefore, even in healthy subjects without hiatal hernias, temporary hiatal hernias occur during TLESR [64]. Regarding other mechanisms responsible for acid reflux besides TLESR (swallow-induced, strain, and free reflux), acid reflux increases when the acid pocket is present in the hernia sac [64]. Thus, the acid pocket is considered to be closely related to postprandial acid reflux, and evaluations to make the “acid pocket” a target for the treatment of GERD have begun.

Regarding the relationship between hiatal hernias and esophageal acid clearance, the esophageal bolus clearance of acid was found to be significantly delayed in patients with a hernia sac [65]. The acid pocket in the hernia sac is also considered to be involved in the delayed esophageal bolus clearance of acid. As shown in the Fig. 3, pressure is higher in the hernia sac than in the esophagus. If the acid pocket is present in the hernia sac, acid easily refluxes into the esophagus during LES relaxation after swallowing due to the pressure gradient between the hernia sac and esophagus. The repetition of this phenomenon with each swallow delays the esophageal bolus clearance of acid.

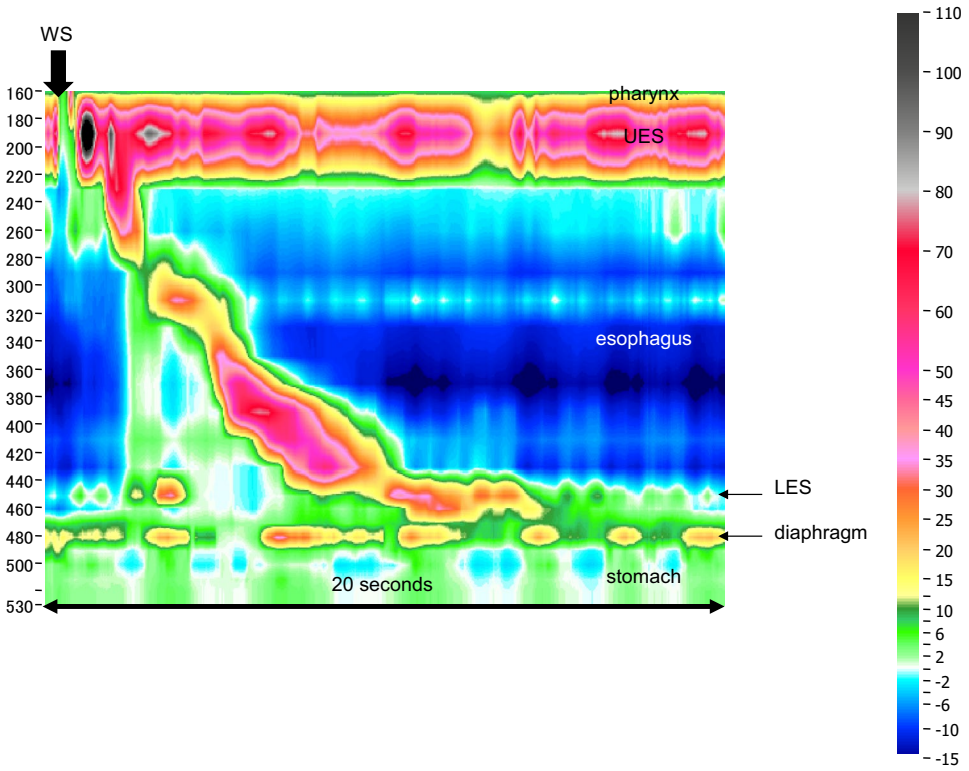

Fig. 3 High-resolution manometric recordings after water swallowing (WS) in a patient with a hiatal hernia. The pressure in the hernia sac after swallowing is higher than esophageal pressure. If acid is present in the hernia sac, it easily refluxes into the esophagus during LES relaxation after swallowing due to the pressure gradient between the sac and esophagus. This is a factor involved in excessive esophageal acid exposure, which is a cause of reflux esophagitis

Conclusions

TLESR is a major mechanism responsible for acid reflux, but is not necessarily accompanied by acid reflux. Acid reflux during TLESR and the delayed esophageal bolus clearance of acid are important causes of excessive esophageal acid exposure. The presence of an acid pocket in the hernia sac has been identified as a factor that contributes to acid reflux episodes during TLESR. In GERD patients, the acid pocket may migrate upwards and reach the esophageal side of the EGJ.

Compliance with ethical standards

Ethical Statement All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1964 and later versions. Informed consent was obtained from all patients included in the cited studies.

Conflict of interest The authors report no conflicts of interest.

References

1. Iwakiri K, Kinoshita Y, Habu Y, et al. Evidence-based clinical practice guidelines for gastroesophageal reflux disease 2015. J Gastroenterol. 2016;51:751–67.
2. Mizuno H, Matsuhashi N, Sakaguchi M, et al. Recent effectiveness of proton pump inhibitors for severe reflux esophagitis: the first multicenter prospective study in Japan. J Clin Biochem Nutr. 2015;57:233–8.
3. Lundell LR, Dent J, Bennett JR, et al. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. Gut. 1999;45:172–80.
4. Iwakiri K, Sakamoto C. Pathophysiology of gastroesophageal reflux disease: mitility factor. Jpn J Gastroenterol. 2003;100:1084–94 **(in Japanese)**.
5. Iwakiri K. The role of excessive esophageal acid exposure in patients with gastroesophageal reflux disease. Clin J Gastroenterol. 2009;2:371–9.
6. Holloway RH. The anti-reflux barrier and mechanisms of gastro-oesophageal reflux. Baillieres Best Pract Res Clin Gastroenterol. 2000;14:681–99.
7. Mittal RK, Holloway RH, Penagini R, et al. Transient lower esophageal sphincter relaxation. Gastroenterology. 1995;109:601–10.
8. Schoeman MN, Tippett MD, Akkermans LM, et al. Mechanisms of gastroesophageal reflux in ambulant healthy human subjects. Gastroenterology. 1995;108:83–91.
9. Dodds WJ, Dent J, Hogan WJ, et al. Mechanisms of gastroesophageal reflux in patients with reflux esophagitis. N Engl J Med. 1982;307:1547–52.
10. Dent J, Holloway RH, Toouli J, et al. Mechanisms of lower esophageal sphincter incompetence in patients with symptomatic gastrooesophageal reflux. Gut. 1988;29:1020–8.
11. Mittal RK, McCallum RW. Characteristics and frequency of transient relaxations of the lower esophageal sphincter in patients with reflux esophagitis. Gastroenterology. 1988;95:593–9.
12. Dodds WJ, Kahrilas PJ, Dent J, et al. Analysis of spontaneous gastroesophageal reflux and esophageal acid clearance in patients with reflux esophagitis. J Gastrointest Motil. 1990;2:79–89.

13. Sifrim D, Holloway R, Silny J, et al. Composition of the postprandial refluxate in patients with gastroesophageal reflux disease. Am J Gastroenterol. 2001;96:647–55.
14. Sano H, Iwakiri K, Kawami N, et al. Mechanisms of acid reflux and how refluxed Acid extends proximally in patients with non-erosive reflux disease. Digestion. 2014;90:108–15.
15. Mittal RK, Fisher MJ. Electrical and mechanical inhibition of the crural diaphragm during transient relaxation of the lower esophageal sphincter. Gastroenterology. 1990;99:1265–8.
16. Hayashi Y, Iwakiri K, Kotoyori M, et al. Mechanisms of acid gastroesophageal reflux in the Japanese population. Dig Dis Sci. 2008;53:1–6.
17. Iwakiri K, Hayashi Y, Kotoyori M, et al. Transient lower esophageal sphincter relaxations (TLESRs) are the major mechanism of gastroesophageal reflux but are not the cause of reflux disease. Dig Dis Sci. 2005;50:1072–7.
18. Lidums I, Lehmann A, Checklin H, et al. Control of transient lower esophageal sphincter relaxations and reflux by the $GABA_B$ agonist baclofen in normal human subjects. Gastroenterology. 2000;118:7–13.
19. Zhang Q, Lehmann A, Rigda R, et al. Control of transient lower oesophageal sphincter relaxations and reflux by the $GABA_B$ agonist baclofen in patients with gastro-oesophageal reflux disease. Gut. 2002;50:19–24.
20. Holloway RH, Hongo M, Berger K, et al. Gastric distention: a mechanism for postprandial reflux. Gastroenterology. 1985;89:779–84.
21. Wyman JB, Dent J, Heddle R, et al. Control of belching by the lower oesophageal sphincter. Gut. 1990;31:639–46.
22. Holloway R, Kocyan FP, Dent J, et al. Provocation of transient lower esophageal sphincter relaxations by meals in patients with symptomatic gastroesophageal reflux. Dig Dis Sci. 1991;36:1034–9.
23. Penagini R, Bartesaghi B, Conte D, et al. Rate of transient lower oesophageal sphincter relaxations of healthy humans after eating a mixed nutrient meal: time course and comparison with fasting. Eur J Gastroenterol Hepatol. 1992;4:35–8.
24. Wu JC, Mui LM, Cheung CM, et al. Obesity is associated with increased transient lower esophageal sphincter relaxation. Gastroenterology. 2007;132:83–9.
25. Franzi SJ, Martin CJ, Cox MR, et al. Response of canine lower esophageal sphincter to gastric distension. Am J Physiol. 1990;159:G380–5.
26. Iwakiri K, Kobayashi M, Kotoyori M, et al. Relationship between postprandial esophageal acid exposure and meal volume and fat content. Dig Dis Sci. 1996;41:926–30.
27. Becker DJ, Sinclair J, Castell DO, et al. A comparison of high and low fat meals on postprandial esophageal acid exposure. Am J Gastroenterol. 1989;84:782–6.
28. Holloway RH, Lyrenas E, Ireland A, et al. Effect of intraduodenal fat on lower oesophageal sphincter function and gastro-oesophageal reflux. Gut. 1998;42:449–53.
29. Penagini R, Mangano M, Bianchi PA. Effect of increasing The fat content but not The energy load of a meal on gastro-oesophageal reflux and lower oesophageal sphincter motor function. Gut. 1998;42:330–3.
30. Freidin N, Mittal RK, McCallum RW, et al. Does body posture affect the incidence and mechanism of gastro-oesophageal reflux? Gut. 1991;32:133–6.
31. Dent J, Dodds WJ, Friedman RH, et al. Mechanism of gastroesophageal reflux in recumbent asymptomatic subjects. J Clin Invest. 1980;65:256–67.
32. Freidin N, Fisher MJ, Taylor W, et al. Sleep and nocturnal acid reflux in normal subjects and patients with reflux oesophagitis. Gut. 1991;32:1275–9.
33. Cox MR, Martin CJ, Dent J, et al. Effect of general anaesthesia on transient lower oesophageal sphincter relaxations in the dog. Aust NZ J Surg. 1988;58:825–30.
34. Martin CJ, Patrikios J, Dent J. Abolition of gas reflux and transient lower esophageal sphincter relaxation by vagal blockade in the dog. Gastroenterology. 1986;91:890–6.
35. Staunton E, Smid SD, Dent J, et al. Triggering of transient LES relaxations in ferrets: role of sympathetic pathways and effects of baclofen. Am J Physiol. 2000;279:G157–62.
36. Neuhuber WL. Sensory vagal innervation of the rat esophagus and cardia: a light and electron microscopic anterograde tracing study. J Auton Nerv Syst. 1987;20:243–55.
37. Altschuler SM, Bao XM, Bieger D, et al. Viscerotopic representation of the upper alimentary tract in the rat: sensory ganglia and nuclei of the solitary and spinal trigeminal tracts. J Comp Neurol. 1989;283:248–68.
38. Kalia M, Sullivan JM. Brainstem projections of sensory and motor components of the vagus nerve in the rat. J Comp Neurol. 1982;211:248–65.
39. Barber WD, Burks TF. Brain stem response to phasic gastric distension. Am J Physiol. 1983;245:G242–8.
40. Hornby P. How are transient LES relaxations triggered? In: Guili R, Galmiche J-P, Jamieson GG, Scarpignato C, editors. The esophagogastric junction. Paris: John Libbey, Eurotext; 1988. p. 62–72.
41. Rinaman L, Card JP, Schwaber JS, et al. Ultrastructural demonstration of a gastric monosynaptic vagal circuit in the nucleus of the solitary tract in rat. J Neuosci. 1989;9:1985–96.
42. Hopkins DA. Ultrastructure and synaptology of the nucleus ambiguus in the rat: the compact formation. J Comp Neurol. 1995;360:705–25.
43. Sang Q, Goyal RK. Lower esophageal sphincter relaxation and activation of medullary neurons by subdiaphragmatic vagal stimulation in the mouse. Gastroenterology. 2000;119:1600–9.
44. Mittal RK, Balaban DH. The esophagogastric junction. N Engl J Med. 1997;27(336):924–32.
45. Dent J, Dodds WJ, Friedman RH, et al. Mechanism of gastroesophageal reflux in recumbent asymptomatic subjects. J Clin Invest. 1980;65:256–67.
46. Iwakiri K, Kawami N, Sano H, et al. Mechanisms of excessive esophageal acid exposure in patients with reflux esophagitis. Dig Dis Sci. 2009;54:1686–92.
47. Helm JF, Dodds WJ, Riedel DR, et al. Determinants of esophageal acid clearance in normal subjects. Gastroenterology. 1983;85:607–12.
48. Helm JF, Dodds WJ, Pelc LR, et al. Effect of esophageal emptying and saliva on clearance of acid from the esophagus. N Engl J Med. 1984;31:284–8.
49. Kahrilas PJ, Dodds WJ, Hogan WJ, Kern M, Arndorfer RC, Reece A. Esophageal peristaltic dysfunction in peptic esophagitis. Gastroenterology. 1986;91:897–904.
50. Kahrilas PJ, Dodds WJ, Hogan WJ. Effect of peristaltic dysfunction on esophageal volume clearance. Gastroenterology. 1988;94:73–80.
51. Iwakiri K, Sugiura T, Hayashi Y, et al. Esophageal motility in Japanese patients with Barrett's esophagus. J Gastroenterol. 2003;38:1036–41.
52. Sugiura T, Iwakiri K, Kotoyori M, et al. Relationship between severity of reflux esophagitis according to the Los Angeles classification and esophageal motility. J Gastroenterol. 2001;36:226–30.
53. Bredenoord AJ, Fox M, Kahrilas PJ, et al. International High Resolution Manometry Working Group. Chicago classification criteria of esophageal motility disorders defined in high resolution esophageal pressure topography. Neurogastroenterol Motil. 2012;24(Suppl 1):57–65.

54. Iwakiri K, Hayashi Y, Kotoyori M, et al. Defective triggering of secondary peristalsis in patients with non-erosive reflux disease. J Gastroenterol Hepatol. 2007;22:2208–11.
55. Holloway RH, Penagini R, Schoeman MN, Dent J. Effects of cisapride on secondary peristalsis in patients with gastroesophageal reflux disease. Am J Gastroenterol. 1999;94:799–803.
56. Kahrilas PJ, Shi G, Manka M, et al. Increased frequency of transient lower esophageal sphincter relaxation induced by gastric distension in reflux patients with hiatal hernia. Gastroenterology. 2000;118:688–95.
57. van Herwaarden MA, Samson M, Smout AJ. Excess gastroesophageal reflux in patients with hiatus hernia is caused by mechanisms other than transient LES relaxations. Gastroenterology. 2000;119:1439–46.
58. Kahrilas PJ, McColl K, Fox M, et al. The acid pocket: a target for treatment in reflux disease? Am J Gastroenterol. 2013;108:1058–64.
59. Fletcher J, Wirz A, Young J, et al. Unbuffered highly acidic gastric juice exists at the gastroesophageal junction after a meal. Gastroenterology. 2001;121:775–83.
60. Clarke AT, Wirz AA, Manning JJ, et al. Severe reflux disease is associated with an enlarged unbuffered proximal gastric acid pocket. Gut. 2008;57:292–7.
61. Pandolfino JE, Zhang Q, Ghosh SK, et al. Acidity surrounding the squamocolumnar junction in GERD patients: "acid pocket' versus "acid film". Am J Gastroenterol. 2007;102:2633–41.
62. Beaumont H, Bennink RJ, de Jong J, et al. The position of the acid pocket as a major risk factor for acidic reflux in healthy subjects and patients with GORD. Gut. 2010;59:441–51.
63. Bredenoord AJ, Weusten BL, Timmer R, et al. Intermittent spatial separation of diaphragm and lower esophageal sphincter favors acidic and weakly acidic reflux. Gastroenterology. 2006;130:334–40.
64. Lee YY, Whiting JG, Robertson EV, et al. Kinetics of transient hiatus hernia during transient lower esophageal sphincter relaxations and swallows in healthy subjects. Neurogastroenterol Motil. 2012;24:e539–990.
65. Sloan S, Kahrilas PJ. Impairment of esophageal emptying with hiatal hernia. Gastroenterology. 1991;100:596–605.