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REVIEW

The Acid Pocket: A Target for Treatment in Reflux Disease?

Peter J. Kahrilas, MD[1], Kenneth McColl, MD[2], Mark Fox, MD[3], Lisa O'Rourke, PhD[4], Daniel Sifrim, MD[5], Andre J.P.M. Smout, MD[6] and Guy Boeckxstaens, MD[7]

The nadir esophageal pH of reflux observed during pH monitoring in the postprandial period is often more acidic than the concomitant intragastric pH. This paradox prompted the discovery of the "acid pocket", an area of unbuffered gastric acid that accumulates in the proximal stomach after meals and serves as the reservoir for acid reflux in healthy individuals and gastroesophageal reflux disease (GERD) patients. However, there are differentiating features between these populations in the size and position of the acid pocket, with GERD patients predisposed to upward migration of the proximal margin onto the esophageal mucosa, particularly when supine. This upward migration of acid, sometimes referred to as an "acid film", likely contributes to mucosal pathology in the region of the squamocolumnar junction. Furthermore, movement of the acid pocket itself to a supradiaphragmatic location with hiatus hernia increases the propensity for acid reflux by all conventional mechanisms. Consequently, the acid pocket is an attractive target for GERD therapy. It may be targeted in a global way with proton pump inhibitors that attenuate acid pocket development, or with alginate/antacid combinations that colocalize with the acid pocket and displace it distally, thereby demonstrating the potential for selective targeting of the acid pocket in GERD.

Am J Gastroenterol 2013; 108:1058–1064; doi:10.1038/ajg.2013.132; published online 30 April 2013

INTRODUCTION

Increased acid reflux after meals is a hallmark of gastroesophageal reflux disease (GERD) and the cause of associated symptoms, particularly heartburn and regurgitation (1,2). Chronic acid exposure also predisposes to associated pathologies, including esophageal ulcer, esophageal stricture, Barrett's esophagus, and esophageal adenocarcinoma (1). As the severity of esophageal symptoms and mucosal damage is related to the pH of the gastric refluxate, intragastric pH is of particular significance, especially in the proximal stomach, the most immediate source of refluxate.

Despite meal-stimulated acid secretion, intragastric pH is at its highest after a meal owing to the buffering effect of food (3). Thus, it is somewhat paradoxical that most acid reflux episodes and heartburn occur during the postprandial period (2,4). It was this paradox that prompted Fletcher *et al.* to carry out a series of experiments in 2001, wherein they detected an area of unbuffered, highly acidic, gastric juice at the esophagogastric junction (EGJ) in the postprandial period (5). They performed a stepwise pull-through with a pH electrode from the proximal stomach, across the EGJ, and into the esophagus in 10 healthy volunteers during fasting and after a large high-fat meal (5). In the fasting state, average intragastric pH was 1.4. After a meal, intragastric pH increased to 4.4, but was still pH 1.6 in the region adjacent to the gastroesophageal pH step-up point. This postprandial phenomenon of newly secreted acid layering on top of the less acidic chyme was termed the "acid pocket" (5).

ACID POCKET ETIOLOGY

Fletcher *et al.* hypothesized that the acid pocket occurred as a result of meal-stimulated acid mixing poorly with the chyme in the proximal stomach. Following a meal, proximity to the acid-secreting mucosa means that the periphery of the gastric lumen is the most acidic and the buffering effect of food is greatest at the center. From a motility perspective, the proximal stomach is relatively quiescent after a meal, being the region where gastric accommodation facilitates storage, thus allowing gastric secretions to form a distinct layer above the chyme (6). In contrast, after a meal peristaltic gastric contractions originate high on the greater curvature in the pacemaker area and become visually evident at the junction between the body of the stomach and the antrum. Gastric contractions are increasingly occlusive as they traverse the antrum, eventually driving gastric contents against the pylorus (7–9). This process mixes gastric secretions with food,

[1]Division of Gastroenterology and Hepatology, Department of Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, USA; [2]Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK; [3]NIHR Biomedical Research Unit for Gastrointestinal and Liver Diseases, Nottingham University Hospitals, Nottingham, UK; [4]Mash Health, London, UK; [5]Barts and the London School of Medicine and Dentistry, University of London, Centre for Digestive Diseases, Wingate Institute for Neurogastroenterology, London, UK; [6]Department of Gastroenterology and Hepatology, Academic Medical Centre, Amsterdam, The Netherlands; [7]Department of Gastroenterology, Translational Research Center for Gastrointestinal Disorders (TARGID), University Hospital Leuven, Catholic University Leuven, Leuven, Belgium. **Correspondence:** Peter J. Kahrilas, MD, Division of Gastroenterology and Hepatology, Department of Medicine, Feinberg School of Medicine, Northwestern University, 676 N. St. Clair Street, 14th Floor, Chicago, Illinois 60611, USA. E-mail: p-kahrilas@northwestern.edu

Received 10 January 2013; accepted 26 March 2013

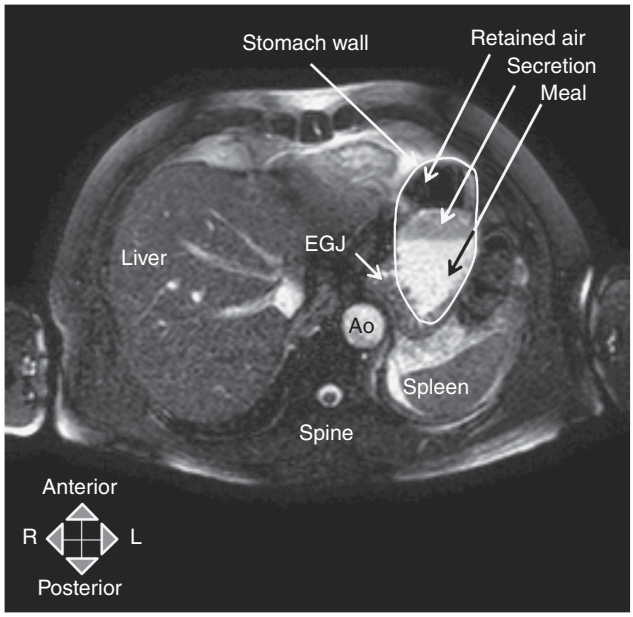

Figure 1. Magnetic resonance imaging (MRI) transverse section of abdomen at the T10 level of a healthy subject in the prone position 30 min after ingestion of a homogeneous 400 ml liquid nutrient test meal (300 kcal, 4.5 g fat/100 ml), stable in the acid environment of the stomach. The meal appears bright owing to paramagnetic contrast (Gadolinium-DOTA). A layer containing a much lower concentration of contrast is visible above the liquid meal. Validation studies have demonstrated that this is a layer of unbuffered gastric secretion that has not mixed with the meal in the proximal stomach (6,56). (Image courtesy of Mark Fox, Helen Parker, NIHR BRU, Nottingham, UK and Caroline Hoad, Carolyn Costigan, Sir Peter Mansfield MRI Centre, University of Nottingham, UK.). EGJ, esophagogastric junction.

and a combination of mechanical and chemical digestion in the distal stomach breaks down solid material into tiny particles before passage into the duodenum (10,11). This division of function explains the presence of a region (pocket) of low pH located between the higher pH environs of the esophagus and the meal in the proximal stomach, with effective mixing of the acid and chyme observed only in the more distal stomach.

Since the description of the acid pocket, the pH environment within the stomach has attracted much interest. Numerous studies have confirmed the presence of the acid pocket (6,12–20), investigated its precise location (13,15) and its potential role in the pathogenesis of GERD (13,15,19). It has been studied using a variety of different techniques, including pH pull-through (12,13,15–17), multiple stationary pH electrodes (14,17), single-photon emission computed tomography following injection of [^{99M}Tc] pertechnetate (18,19) and, most recently, magnetic resonance imaging (MRI; **Figure 1**) (6,20).

Good correlation has been found between the pH within the acid pocket and the nadir refluxate pH, supporting the concept of the acid pocket as a source for postprandial acid reflux (21). The time course of the acid pocket also correlates well with the prevalence of postprandial acid reflux events, which are reported to occur most frequently in the first postprandial hour, in both healthy volunteers and GERD patients (19). Grigolon *et al.* (22) timed the first onset of the acid pocket using a BRAVO pH capsule 2 cm below the lower esophageal sphincter (LES) and found the median time for onset of the acid pocket was 14 min. A number of other studies corroborate this and have demonstrated that the pocket persists for up to 90 min after meals (14,17,19). In one study, real-time recording of fasting and postprandial luminal pH with a 12 pH electrode assembly allowed close observation of the dynamic changes to esophageal and stomach pH over time (14). Recordings clearly demonstrated that the gastric cardia paradoxically became more acidic after a meal while the rest of the stomach became less acidic. In this case, the acid pocket was first observed 17 min after the meal, progressively lengthening and becoming more acidic until 44 min (**Figure 2**). At 48 min, a highly acidic esophageal reflux event was observed at a time when the only region of the stomach with equal acidity was the acid pocket (14).

THE ACID POCKET IN HEALTH AND DISEASE

Reflux episodes are conventionally measured 5 cm proximal to the proximal margin of the LES, despite the fact that mucosal pathology (erosions and metaplasia) is usually limited to the distal esophageal mucosa. However, recent evidence suggests significantly greater acid exposure in the more distal and "intrasphincteric" segment of the esophagus both in GERD patients and patients with normal esophageal acid exposure at the 5 cm position (13,23–28). Fletcher *et al.* found that 24-h esophageal acid exposure was about six times greater at 0.5 cm compared with 5.5 cm proximal to the squamocolumnar junction (SCJ) (11.7 vs. 1.8%; $P<0.001$) (24). This intrasphincteric acid exposure occurs mainly after meals at a time when the EGJ is relatively weak and can oscillate between a hernia and non-hernia configuration, especially in patients with reflux disease (29). Acid exposure adjacent to the SCJ is less likely than conventionally measured reflux to be symptomatic (24); however, it is potentially of great pathophysiological significance with respect to the mucosa and likely to involve the acid pocket. Intrasphincteric acid exposure may explain how metaplasia of the distal esophagus is most prevalent at, and immediately proximal to, the SCJ and can occur in subjects without conventional evidence of reflux disease. It could also account for short-segment Barrett's esophagus being several times more prevalent than long-segment Barrett's esophagus (30). It is provocative to note that, as bile acids have been detected within the acid pocket of healthy volunteers (31,32), this may explain why short-segment Barrett's esophagus has no association with GERD symptoms (33). However, there are no data yet to support such speculation. The potential relevance of the presence of bile for GERD is summarized in a recent systematic review suggesting that bile acids contribute to the pathogenesis of GERD symptoms, esophagitis, and Barrett's metaplasia (34).

An increase in the number of transient lower esophageal relaxations (TLESRs) after meals is a well-established mechanism for conventional postprandial gastroesophageal reflux in both healthy individuals and patients with GERD (35,36). However, as there is no consistent difference in the frequency of TLESRs in health and disease, increased esophageal acid exposure in GERD usually can-

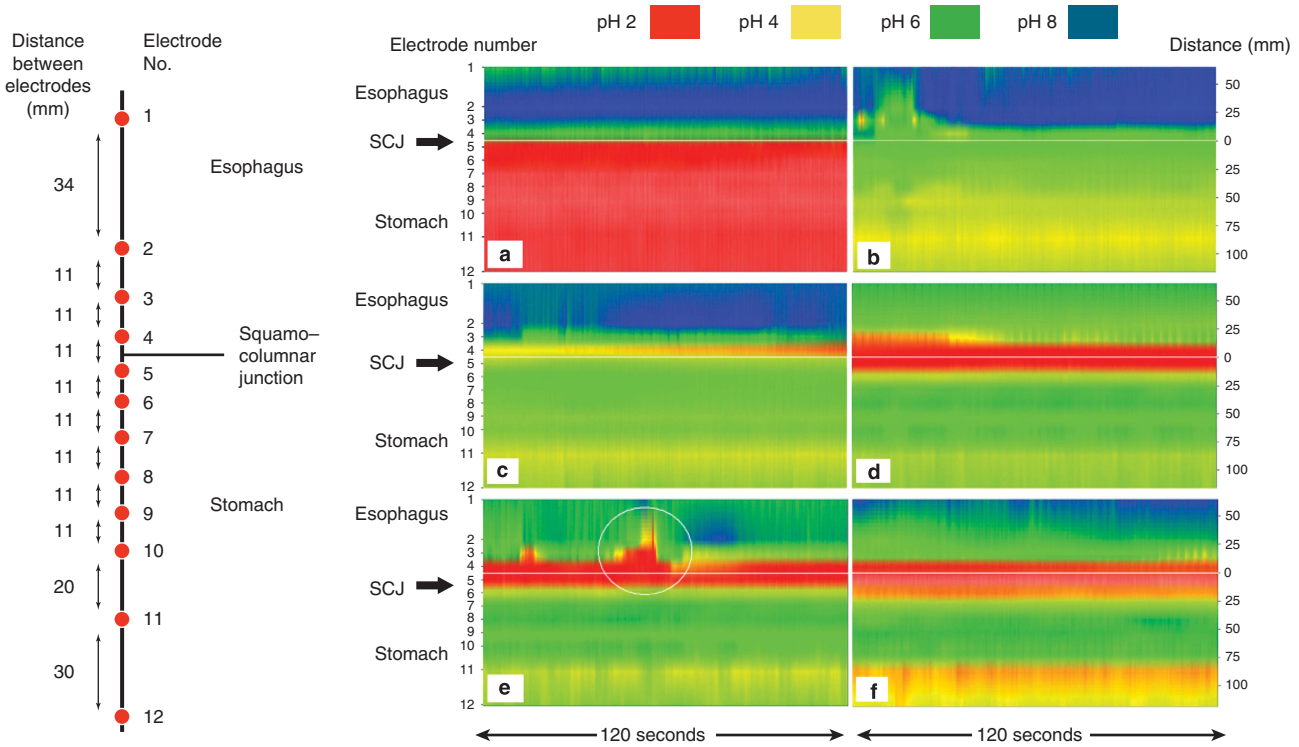

Figure 2. Characterization of acidity in the distal esophagus and proximal stomach under fasting conditions and in response to a large meal using high-resolution pH-metry in healthy subjects (14). The left panel shows the position of the 12-electrode catheter relative to the squamocolumnar junction (SCJ). The catheter was clipped to the SCJ with an endoclip using a loop tied between electrodes 4 and 5, 10.5 cm proximal to electrode 12 at the catheter tip. The right panel illustrates pH contour plots (120 s duration each) of the high-resolution 12-electrode pH-metry (**a**) in the fasting state, showing marked intragastric acidity, (**b**) 3 min after the meal, showing intragastric buffering by food, (**c**) 17 min after the meal, showing emergence of the acid pocket at the esophagogastric junction, (**d**) 43.5 min after the meal, showing acid pocket enlargement, (**e**) 47.5 min after the meal, showing an acid reflux episode from the acid pocket (circled) despite simultaneous distal intragastric buffering, and at (**f**) 73.5 min after the meal simultaneously recording the proximal acid pocket and distal gastric acidity.

not be attributed to an increased number of TLESRs (19,37,38). Rather, distinguishing factors are the consequences of TLESRs; reflux is twice as likely to be acidic (pH < 4) than weakly acidic in GERD patients whereas healthy volunteers are more likely to reflux gas or weakly acidic liquid (37,39). Furthermore, once reflux events occur, the process of acid clearance is prolonged in GERD patients (38). It is an attractive proposition that changes to the acid pocket in GERD may account for some of these differences. The acid pocket is ubiquitous, forming in both healthy individuals and GERD patients (13,15), but increasing evidence suggests that alterations to its location and/or distribution may favor acid reflux from the pocket. As such, alterations to the acid pocket may be a key factor differentiating GERD patients from control subjects.

ACID POCKET EXTENSION

In the original study by Fletcher *et al.*, the acid pocket was reported to extend across the SCJ in healthy volunteers (5). That observation was difficult to reconcile with the fixed location of the LES at the level of the SCJ and its normal barrier function. In retrospect, the proximal extent of the acid pocket was likely overestimated in those experiments owing to non-concurrent pH and manometric measurements and movement of the clips attached to the SCJ with respiration. However, subsequent studies by this group and others found that the proximal margin of the acid pocket does extend into the LES in some circumstances (13,15,19). In fact, migration of the upper border of the acid pocket across the SCJ has been found to be a defining feature of GERD, with pocket extension correlating with GERD/hiatus hernia severity (13,15,19). The terminology gets confusing at this point because although the term "acid pocket" implies an associated volume of acid, this may, or may not, be the case. Within the closed lumen (or sphincter), even minute boluses of acid, as little at 0.05 ml, will acidify the mucosa (40). Normally the pH transition point from gastric to esophageal occurs at, or very close to, the SCJ (41). Hence, if the "acid pocket" traverses the SCJ, it is actually comprised of two conceptually distinct components. Distal to the SCJ is the phenomenon described by Fletcher that has volume associated with it and serves as a reservoir for postprandial reflux. Proximal to the SCJ is a zone of mucosal acidification with no significant associated volume that may be of pathophysiological significance with respect to mucosal pathology and/or reflux symptoms. Pandolfino *et al.* (15) demonstrated that the "acid pocket" extended through the closed LES in GERD patients, particularly in a supine posture, which led the investigators to propose the term

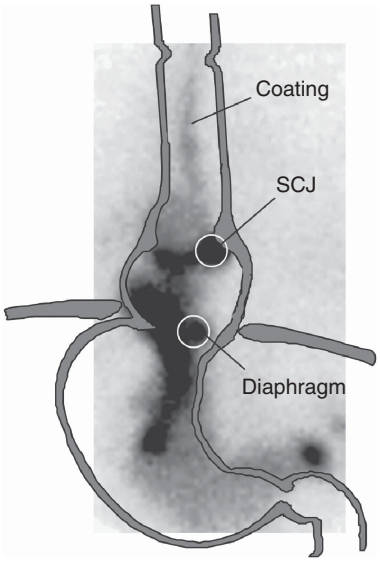

Figure 3. Representative scintigraphic image of the postprandial acid pocket and the squamocolumnar junction (SCJ) in a gastroesophageal reflux disease patient with a large hiatal hernia (19). Technicium pertechnitate was used to visualize the formation and disposition of the acid pocket while radiolabeled clips indicate the locations of the SCJ and the diaphragmatic hiatus. The acid pocket can be seen largely confined to the hernia compartment above the diaphragm. Clear, but less intense, activity in the distal esophagus is observed, suggesting the presence of a thin acid layer coating the esophageal mucosa. This coating was seen in almost half of the test patients with a hiatus hernia ≥3 cm and, when present, the acid layer extended 5.6±0.7 cm above the SCJ.

"acid film" rather than "acid pocket". Regardless, the migration of an acid film across the SCJ onto the intrasphincteric squamous mucosa represents a novel and potentially important mechanism for distal esophageal acid exposure that is directly attributable to the acid pocket. However, the specificity of this finding for symptomatic GERD remains to be defined in larger studies of more fully characterized subgroups of GERD patients.

Beaumont *et al.* (19) subsequently confirmed that a discrete volume of acid exists in the proximal stomach postprandially. Using scintigraphy, they were able to localize the acid pocket 30 min after a meal, aspirate it, observe the radioactivity disappear, and then observe it reappear 10 min later. The aspirate had a volume of 70 ml and a pH of 1.8. In addition to this pool of acid, and in line with Pandolfino's "acid film" hypothesis, they also observed an acid coating of the distal esophagus, up to 6 cm above the SCJ in GERD patients with a large hiatus hernia (**Figure 3**). Furthermore, direct observation using MRI after a large meal suggests that, in contrast to TLESR-associated reflux that is observed in health and GERD, such proximal acid migration is a phenomenon thus far seen only in GERD patients (42). The cause of acid migration into the esophagus has not been established; however, initial observations suggest that these events occur only when LES pressure is very low and may be attributable to a primary abnormality of sphincter closure with resultant increased thickness of the luminal wet layer. Data from a mathematical modeling study suggest that fluid migration into the sphincter is very sensitive to the thickness of luminal

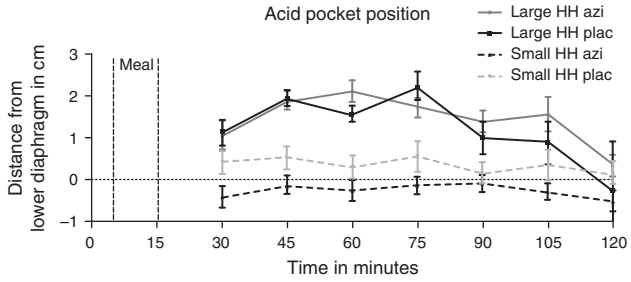

Figure 4. Scintigraphic assessment of the effect of azithromycin on acid pocket position relative to the crural diaphragm in gastroesophageal reflux disease patients, with large (≥3 cm) and small (<3 cm) hiatal hernia (47). Azithromycin resulted in a more distal position of the acid pocket compared with placebo in patients with small hiatal hernia, but not in those with large hiatal hernia.

wet layer and that values exceeding 0.4 mm facilitate the tracking of acid into the distal esophagus (43).

ACID POCKET AND HIATUS HERNIA

Hiatus hernia is intimately involved in the pathogenesis of GERD, impairing both LES function and esophageal clearance, thereby increasing esophageal acid exposure (44,45). Studies suggest that the presence of hiatus hernia may also influence reflux disease through effects on the size and position of the acid pocket. Clarke *et al.* (13) demonstrated that reflux patients had longer acid pockets than healthy volunteers, attributable to the proximal migration of the EGJ, in other words, the presence of hiatus hernia. Beaumont *et al.* (19) studied the size and location of the acid pocket in healthy volunteers and GERD subjects with small and large hiatus hernia. Consistent with the findings of Clarke, they found longer acid pockets in GERD patients. However, they proposed that it was the position, not the length, of the acid pocket that was important. When the acid pocket was located above the diaphragm or extended into the hiatal opening, 70–85% of all TLESRs were accompanied by acidic reflux. In contrast, when the acid pocket was located below the diaphragm, only 7–20% of TLESRs were accompanied by acid reflux (19). Multivariate regression analysis revealed that both the presence of a hiatus hernia and positioning of the acid pocket above the diaphragm were major independent risk factors for acidic reflux to occur during a TLESR (19). Interestingly, even in healthy volunteers, most acidic reflux occurred when the acid pocket extended into the hiatus. This can be explained by episodes of intermittent spatial separation of the LES and crural diaphragm reported previously by Bredenoord *et al.* (29) during prolonged high-resolution manometry studies. Assuming that the acid pocket migrates upwards with the LES, a situation comparable to a hernia would result promoting acid reflux. In fact, continuous postprandial monitoring of the location of the EGJ in healthy volunteers confirmed that during TLESRs there was marked proximal movement of the EGJ by a median of 4.3 cm, representing significant herniation (46). The Bredenoord and Beaumont studies also reported that spatial separation between the LES and crural diaphragm increases the risk

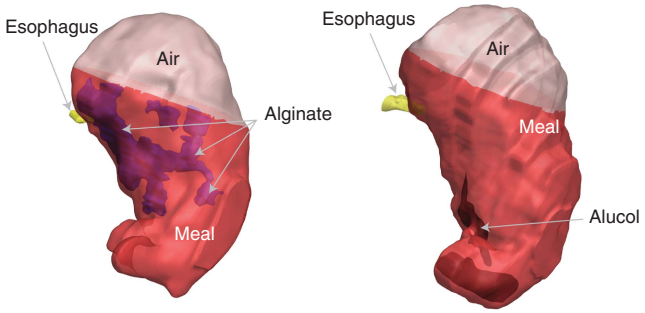

Figure 5. 3D (three-dimensional) reconstruction of magnetic resonance imaging images of the stomach postprandially showing the disposition of an administered alginate/antacid combination (Gaviscon Advance; Reckitt Benckiser, UK) or antacid (Alucol; Wander, Berne, Switzerland) in healthy volunteers in the right lateral supine position tilted to 30°. Fifteen minutes after administration, the alginate/antacid formed a clot in the region of the esophagogastric junction and a raft at the air–meal interface, while the antacid sank to the distal stomach (51). (Images courtesy of Jelena Curcic, Institute for Biomedical Engineering, Swiss Federal Institute for Technology and Mark Fox, Division of Gastroenterology, University Hospital, Zurich, Switzerland. 3D image reconstruction courtesy of Anupam Pal, Indian Statistical Institute, Kolkata, India.)

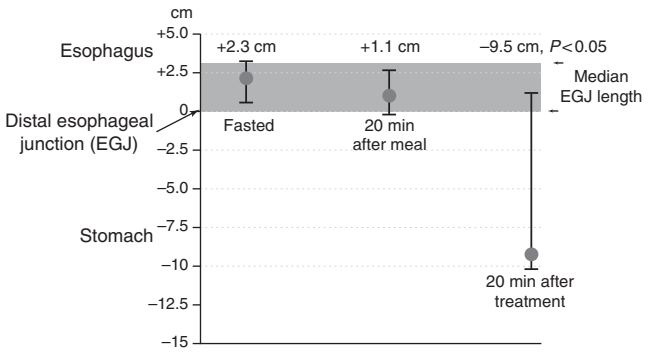

Figure 6. Assessment of the ability of an alginate/antacid formulation (Gaviscon Double Action; Reckitt Benckiser) to neutralize and/or displace the acid pocket in 10 gastroesophageal reflux disease (GERD) patients (55). The proximal pH transition point relative to the distal margin of the manometrically monitored esophagogastric junction (EGJ) is shown during fasting and postprandially, before and after dosing with the alginate/antacid combination. The location of the proximal pH transition point demarcated an acidified segment that extended from the proximal stomach into the EGJ and esophagus. The unbuffered segment persisted postprandially. Gaviscon neutralized the acidified segment, eliminating the acid pocket in the majority of the GERD patients, indicated by the significant relocation of the pH transition point away from the EGJ. Data shown as medians and interquartile ranges. *$P<0.05$ vs. fasted/postprandial.

for reflux by any mechanism, such as swallowing and straining, not just TLESRs. The evidence from these studies suggests that structural changes that alter the dynamics of the acid pocket may be a major factor for increased acid reflux in GERD. In line with this, MRI reveals subtle anatomical differences in GERD patients vs. healthy volunteers. These changes create structural disruption of the EGJ, albeit in a less severe manner than hiatus hernia (42). The insertion angle of the esophagus is more obtuse than that in healthy volunteers, with the position of insertion being more displaced from the midline, offering less resistance to flow from the acid pocket when the stomach is full. These observations suggest that overt hiatus hernia is the endpoint of progressive degradation of EGJ anatomy, but it is not necessarily the starting point of clinical relevance.

THERAPEUTIC AGENTS, AND THE ACID POCKET

Prokinetic agents that increase proximal tone and promote gastric emptying may disrupt the acid pocket. Boecxstaens *et al.* (32) demonstrated that the administration of the promotility drug erythromycin suppressed the acid pocket, while sumatriptan (a gastric relaxant) had an opposite effect. Similarly, Rohof *et al.* (47) have shown that the prokinetic agent azithromycin can displace the acid pocket to a more distal location (**Figure 4**). In patients with a small hiatus hernia, azithromycin reduced hernia size and increased the amount of time it was in the reduced state. Acid reflux was also reduced in these patients (38% to 17%) while the total number of reflux events was unchanged; no effects were observed in patients with large hiatus hernia (47). The gamma-aminobutyric acid agonist, baclofen, has also been shown to significantly reduce the extent of the acid pocket in healthy volunteers. The distance above the LES was much shorter after baclofen treatment (0.3 cm vs. 1.6 cm after 1 h), likely owing to increased LES pressure (48). More recently, data have been presented suggesting that baclofen may reduce the insertion angle of the esophagus in GERD patients, which may also help protect from reflux (42).

Three studies have demonstrated that the acid pocket persists with proton pump inhibitor treatment, but that the pH is increased (12,21,49). A recent study assessing effects on the size and position of the acid pocket after proton pump inhibitor treatment demonstrated that while there was not a major change in position, the acid pocket was smaller and the pH increased from 1 to 4 (21). There was a clear correlation between pocket pH and refluxate pH, indicating that the proton pump inhibitor effect on acid pocket pH may contribute to the effectiveness of these drugs in GERD management.

Alginate preparations precipitate on contact with gastric acid and have been shown to suppress acid reflux in adults and infants (50–54). Recent observations of an alginate/antacid combination using MRI show formation of a raft at the air–meal interface after a liquid meal and formation of a clot between the EGJ and solid meal, exactly where the acid pocket would be located (**Figure 5**) (51). The number of reflux events observed after alginate/antacid was half that observed after antacid alone, which was seen by MRI to sink to the distal stomach (51). Along similar lines, Kwiatek *et al.* (55) recently demonstrated that an alginate/antacid combination neutralized the acid layer on top of a meal and profoundly shifted the pH transition point away from the EGJ in the majority of GERD patients studied (**Figure 6**).

SUMMARY

The postprandial acid pocket is clinically important both as a reservoir of gastric acid for gastroesophageal reflux and as a mechanism of distal esophageal mucosal acidification in the postprandial

period. Differences in acid pocket size and location have been observed in health and disease, with GERD patients predisposed to upward migration of the proximal border of the acid pocket across the SCJ onto the distal esophageal mucosa. As this intrasphincteric (and sometimes suprasphincteric) component of the acid pocket occurs within a closed lumen and has minimal associated volume, it has sometimes been termed an "acid film" or "acid coating". The coating of the squamous mucosa is likely to contribute to the high prevalence of mucosal pathology observed adjacent to the SCJ, and the precise mechanisms that facilitate this migration of acid from the pocket warrant further investigation. Furthermore, the anatomical changes conferred by hiatus hernia promote a supradiaphragmatic location of the reservoir portion of the acid pocket, significantly increasing the risk for acid reflux by all conventional mechanisms.

Given the potential clinical relevance of the acid pocket, displacement of the pocket away from the EGJ is an attractive mode of therapy for GERD. In fact, existing agents shown to reduce acid reflux have been found to make alterations to the size, position, or pH of the acid pocket. It is likely that these changes to the acid pocket contribute to their therapeutic benefit, and further reinforces the potential of the acid pocket as a target in reflux disease.

CONFLICT OF INTEREST

Guarantor of the article: Peter J. Kahrilas, MD.

Specific author contributions: Drafting the manuscript: Peter J. Kahrilas and Lisa O'Rourke; all authors discussed the content of the manuscript before drafting, provided critical revision of the manuscript, and approved the submitted draft.

Financial support: None.

Potential competing interests: P.J.K. serves as a paid consultant for EndoGastric Solutions, Ironwood Pharmaceuticals, Reckitt Benckiser, and Torax. He receives grant support from the US National Institute of Health (R01 DC00646) and has received grant support from Reckitt Benckiser. K.M. serves as a paid consultant for GSK and Reckitt Benckiser. M.F. serves as a paid consultant for Reckitt Benckiser and has received grant support from Astra Zeneca and Reckitt Benckiser. L.O. is an employee of Mash Health and assisted with research and medical writing through a grant provided by Reckitt Benckiser. A.J.P.M.S. serves as a paid consultant for Reckitt Benckiser and has received financial support for educational meetings from MMS, Given Imaging, and Shire Movetis. D.S. serves as a paid consultant for GSK, Reckitt Benckiser, and Ono, and receives grant support from Sandhill Scientific. G.B. is supported by grants from the Research Foundation—Flanders (FWO) (Odysseus program, G.0905.07) and the agency for Innovation by Science and Technology (IWT), Belgium, and has received grant support from Reckitt Benckiser.

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