Comparison of Esophageal Function Tests to Investigate the Effect of *Helicobacter Pylori* Infection on Gastroesophageal Reflux Disease (GERD)

ABE 1 Lan Liu  
BC 2 Hongwei Gao  
BCDF 1 Hongjuan Wang  
ABC 1 Kongxi Zhu  
CF 1 Weihua Yu  
BCF 3 Yuan Zhang  
AEG 1 Jianqiang Guo

Corresponding Author: Jianqiang Guo, e-mail: guo_jianqiang@126.com
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Background: The effects of *Helicobacter pylori* (*H. pylori*) infection on gastroesophageal reflux disease (GERD) remain unclear. The aim of this study was to compare the results of clinical esophageal function tests and the effect of *H. pylori* infection on GERD.

Material/Methods: A prospective clinical study included 124 patients diagnosed with GERD (four grades). *H. pylori* infection was determined by gastroscopy and a rapid urease test (RUT) to divide patients into an HP-positive and an HP-negative group. Esophageal function tests included high-resolution manometry (HRM), peristalsis break (PB), and 24-hour pH monitoring (composite pH DeMeester score). Different grades of GERD, with and without *H. pylori* infection, esophageal function test results were analyzed.

Results: The HP-positive group, compared with the HP-negative group with GERD, showed a significantly reduced median PB value (3.41±3.65 vs. 6.18±5.27), reduced PBs >5 cm per ten swallows (2.23±3.05 vs. 4.04±3.70) indicating that *H. pylori* infection improved esophageal peristalsis. During 24-hour esophageal pH monitoring, the HP-positive group showed a significantly reduced percentage of time for esophageal pH <4.0, number of reflux events >5 min, and number of reflux episodes in 24 hours, compared with the HP-negative group. The DeMeester score was significantly increased in the HP-negative group, indicating a higher esophageal acid exposure (9.11±8.15 vs. 24.30±30.27).

Conclusions: *H. pylori* infection improved esophageal peristalsis, enhanced lower esophageal sphincter (LES) pressure, and reduced esophageal acid exposure, which might be protective factors for GERD.

MeSH Keywords: Esophageal pH Monitoring • Gastroesophageal Reflux • *Helicobacter Pylori* • Manometry

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Background

Gastroesophageal reflux disease (GERD) is one of the most prevalent gastrointestinal diseases and is defined as the reflux of stomach contents into the esophagus, which can cause painful symptoms and sometimes, severe complications [1, 2]. GERD is categorized according to the endoscopic findings as reflux esophagitis and non-erosive reflux disease (NERD) [3]. Esophageal adenocarcinoma can arise in patients with GERD and reflux esophagitis, as a result of glandular metaplasia of the normally squamous esophageal epithelium (Barrett’s esophagus) [4]. Recently, worldwide, the morbidity and mortality from esophageal adenocarcinoma have been increasing [5, 6].

*Helicobacter pylori* (*H. pylori*) can colonize the gastric mucosa, giving rise to mild inflammation, but is usually asymptomatic and the eradication of *H. pylori* is now widespread. There continues to be controversy about the appropriate management of *H. pylori* infection in patients with GERD. Many authors recommend *H. pylori* eradication because *H. pylori* infection can accelerate the development of gastric mucosal atrophy, which increases the risk of gastric adenocarcinoma [7]. However, other experts caution against this approach [8], as most epidemiological studies indicate that reflux symptoms, mucosal disease, and esophageal cancer are less common in patients with *H. pylori* infection [9–11]. Whether *H. pylori* infection protects against GERD and the possible mechanisms of this protective effect remain unclear. GERD has a complex and multifactorial pathogenesis [12], which is associated with stomach acidity, and esophageal motility, the protective barrier of the esophagus, and the rate of emptying of the stomach. However, there is the possibility that *H. pylori* infection may influence the development of GERD through some of the causative factors for GERD.

In the 1990s, the use of high-resolution manometry (HRM), capable of monitoring pressure from the pharynx to the stomach, together with pressure topography plotting, was used for the clinical diagnosis of functional esophageal disorders, and in clinical research [13]. HRM has become increasingly important worldwide and is now the standard method for the clinical evaluation of esophageal motility disorders. The 24-hour esophageal pH (24-h pH) monitoring can also be used to observe esophageal gastric acid exposure in a dynamic way.

Based on recently published studies on GERD and the possible role of *H. pylori*, this study was designed to collect data from endoscopic examinations, HRM analysis, and 24-h pH monitoring in GERD patients in the clinic. The aim of this study was to compare the results of clinical esophageal function tests and the effect of *H. pylori* infection on GERD.

Material and Methods

Subjects

A retrospective study was performed using analysis of the data on patients diagnosed gastroesophageal reflux disease (GERD) who underwent endoscopic examination, ambulatory 24-hour esophageal pH monitoring, and esophageal high-resolution manometry (HRM) from January 2013 to December 2016 in the Second Hospital of Shandong University in China. Inclusion criteria were a previous diagnosis of typical reflux symptoms, response to a proton pump inhibitor (PPI), and evidence of reflux esophagitis on endoscopic examination. Exclusion criteria were subjects who had previous gastrointestinal surgery, hiatal hernia, or who were taking medications known to affect gastrointestinal motor function or acid secretion. A total of 124 GERD patients were enrolled in this retrospective study. The study was approved by the Institutional Review Board (IRB) of the Second Hospital of Shandong University.

Endoscopic examination and *Helicobacter pylori* (*H. pylori*) status

Gastroscopy was performed using a GIF H260 endoscope (Olympus, Tokyo, Japan) to identify the status of the gastroesophageal junction and to detect *Helicobacter pylori* (*H. pylori*) infection and to exclude some other organic diseases. Two expert endoscopists performed the evaluation.

GERD was defined endoscopically using the four grades (A to D) of the Los Angeles (LA) classification system (Figure 1). LA grade A represented one or several erosions limited to the mucosal fold(s) and no larger than 5 mm in extent. LA grade B represented one or several erosions limited to the mucosal fold(s) and larger than 5 mm in extent. LA grade C represented erosion(s) extending over mucosal folds, but involving less than three-quarters of the circumference. LA grade D represented confluent erosions extending over more than three-quarters of the circumference (circular defects).

When there was no contraindication for biopsy, the rapid urease test (RUT) was performed as a first-line diagnostic test to assess *H. pylori* status. One biopsy was taken from the corpus and one from the antrum of the stomach [14]. According to the *H. pylori* status, patients were divided into two groups, an *H. pylori*-positive group (HP-positive) and an *H. pylori*-negative group (HP-negative).

The sensitivity of biopsy urease tests is approximately 90%, and specificity is in the range of 95–100% [15]. False-positive tests are unusual, but false-negative results can occur in patients with recent gastrointestinal bleeding or with the use of PPIs, antibiotics, or bismuth-containing compounds, or with...
excessive atrophy and intestinal metaplasia. Therefore, before RUT was performed, patients included in the study had not been treated with antibiotics or bismuth from the previous four weeks and were off PPI therapy from the previous two weeks, before the beginning of the study.

At endoscopy, biopsies were taken from the gastric antrum. Mucosal atrophy, with and without metaplastic epithelial transformation was scored according to the Sydney system for the classification of gastritis, using a visual analog scale (VAS): 0, absent; 1, mild; 2, moderate; 3, severe [16].

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The high-resolution manometry (HRM) protocol

The classification scheme used for high-resolution manometry (HRM) was the Chicago Classification (CC), which has evolved to improve the ability to make manometric diagnoses [17,18]. Subsequent improvements have resulted in the Chicago Classification v3.0 (CC v3.0) [19,20]. HRM was performed in the standard fashion with the subject in the supine position, after at least six hours of fasting, using the Medical Measurement Systems (MMS) (the Netherlands) HRM system. After transnasal placement of the manometry assembly, it was positioned to record from the level of the hypopharynx to the stomach. The manometric protocol also included a 5-minute period to assess basal sphincter pressure with ten swallows of 5 mL of normal saline.
High-resolution manometry (HRM) data analysis

Analysis of HRM data described resting characteristics of the esophageal sphincters, and esophageal motor functions initiated by swallowing (Figure 2). The upper esophageal sphincter (UES) and lower esophageal sphincter (LES) were easily identified as zones of higher pressure. The 4-second integrated relaxation pressure (IRP4s) algorithm took these pressures and averaged the lowest of them, the ‘nadir’ pressure, over 4 continuous or discontinuous seconds. Peristaltic integrity was assessed by measuring gaps in the 20 mmHg pressure contour along the length of the esophagus, between the UES and LES. According to the Chicago classification, small breaks measured between 2–5 cm and large breaks were >5 cm [17,20–22]. As recommended in the Chicago classification (CC v3.0 update), only large breaks were scored [19,20]. The distal contractile integral (DCI), which integrated the length of the smooth muscle of the esophagus (cm), contractile pressure (mmHg), and duration (seconds) of contraction, were used to measure the robustness of peristaltic contraction in the smooth muscle of the esophagus [23]. The ineffective esophageal motility (IEM) has been redefined in the Chicago classification (CC v3.0 update) as the DCI of the swallow <450 mmHg/sec/cm [20,24].

24-hour esophageal pH monitoring

During the study, the patients consumed an unrestricted diet and took no medications that could interfere with the results. The 24-hour esophageal pH monitoring was performed using an antimony pH catheter (Orion-Ohmega, the Netherlands). The sensor was positioned 5 cm above the LES. Continuous pH recording was performed for 24 h. The 24-hour pH monitoring was performed using the composite pH DeMeester score [11], which was used to calculate the following distal pH variables: percentage of total time that the pH was <4, the longest reflux event, the number of reflux events >5 minutes, and the number of reflux episodes in 24 hours. A DeMeester score >14.72 was considered abnormal.

Results

Patient characteristics

A total of 124 patients with gastroesophageal reflux disease (GERD) were enrolled in this study. Of the patients, 24.19% (20/124) were Helicobacter pylori (H. pylori)-positive on rapid urease test (RUT) during endoscopy examination, and 75.81% (94/124) were H. pylori-negative. The mean age of the patients was 49.33 years old in the HP-positive group and 50.99 years old in the HP-negative group, and there was no significant difference in mean ages (P>0.05) (Table 1).

| HP-positive | HP-negative |
|-------------|-------------|
| Numbers (%) | 30 (24.19%) | 94 (75.81%) |
| Gender (M/F) | 10/20 | 36/58 |
| Age (mean, yr) | 49.33±13.00 | 50.99±12.46 |

HP – Helicobacter pylori.

Statistical analysis

Data analysis was performed using SPSS version 16 software (SPSS, IBM, Chicago, IL, USA). Between the two groups (HP-positive and an HP-negative), continuous variables were assessed using the t-test and presented as the mean ± standard deviation (SD). A P-value <0.05 was considered to indicate significance.

High-resolution manometry (HRM) parameters in patients grouped according to H. pylori status

High-resolution manometry (HRM) examination (Figure 3) showed that patients with GERD in the HP-positive group, compared with the HP-negative group, had a higher distal contractile integral (DCI), ineffective esophageal motility (IEM), lower esophageal sphincter (LES) pressure, 4-second integrated relaxation pressure (IRP4s) of the LES pressure, but these differences were not statistically significant (P>0.05). There was a significant difference in median value of peristalsis break (PB) (3.41±3.65 vs. 6.18±5.27) and the number of PB longer than 5 cm per 10 swallows (2.23±3.05 vs. 4.04±3.70) between HP-positive and HP-negative groups, which also support that H. pylori infection can improve esophageal peristalsis (Table 2).

Association between esophageal acid exposure and H. pylori status

During the 24-hour esophageal pH monitoring, the parameters of the HP-positive group including the percentage of the

Table 1. Patient characteristics.
total time that the pH was <4, the longest reflux event, the number of reflux events >5 minutes, and the number of reflux episodes in 24 hours were all lower than in the HP-negative group (P<0.05). The HP-positive group compared with the HP-negative group had a composite pH DeMeester score (9.11±8.15 vs. 24.30±30.27), which was also significantly different between groups (Table 3). These parameters showed the HP-negative group had a higher esophageal acid exposure.
Discussion

Gastroesophageal reflux disease (GERD) has a complex and multifactorial pathogenesis [12], which is associated with stomach acidity, esophageal motility, loss of the protective barrier of the esophagus, and delayed emptying of the stomach. The primary determinants of the severity of GERD are a dysfunctional anti-reflux barrier and impaired esophageal clearance. The anti-reflux mechanisms prevent reflux of gastric contents into the esophagus, and once the gastroesophageal reflux enters the esophagus, peristalsis functions to clear the esophagus of the reflux contents [25]. *Helicobacter pylori* (*H. pylori*) infection can influence GERD through these factors.

An explanation for the protective effect of *H. pylori* infection in GERD is that *H. pylori* infection can cause gastric mucosa atrophy, and impaired acid production [26]. Another hypothesis is that *H. pylori* infection can stimulate the vagus nerve receptor on the fundus and cardia of the stomach, and increase serum gastrin secretion, which can enhance lower esophageal sphincter (LES) pressure, as well as reduce gastric acid and reflux of gastric contents, thereby protecting the esophageal mucosa.

The use of high-resolution manometry (HRM) has made it possible to measure the pressure pattern throughout the entire length of the esophagus with each swallow, from the upper esophageal sphincter (UES) to the lower esophageal sphincter (LES), providing a complete depiction of esophageal motor function [27,28]. HRM has become increasingly important and is now the new worldwide standard for the clinical evaluation of esophageal motility disorders. Esophageal acid exposure can now be dynamically observed by 24-hour esophageal pH monitoring. The present study combined HRM with 24-hour pH monitoring analysis, and provided a set of data useful for investigating the possible mechanisms by which *H. pylori* can affect GERD.

The motility disorders in the esophageal body as classified by the Chicago classification, which focus on the distal esophagus. Ineffective esophageal motility (IEM) has been redefined in the Chicago classification (CC v3.0 update) as the distal contractile integral (DCI) of the swallow <450 mmHg/sec/cm [20,24]. IEM has been found in between 21-49.4% of patients with GERD [29,30]. Prolonged acid clearance from the esophagus with IEM seems the most relevant factor in the development of GERD [31]. In the present study, the DCI was higher in the HP-positive group (837.80±594.97) compared with the HP-negative group (597.48±611.85), and median value of IEM was lower in the HP-positive group (4.00±3.58) compared with the HP-negative group (5.53±3.96), suggesting that *H. pylori* infection can improve esophageal peristalsis. However, this difference was not statistically significant.

The new Chicago classification (CC v3.0 update) has abandoned the concept of a peristalsis defect [20,24]. In 2014, Ribolsi et al. [32] reported that weak peristalsis with a large break was associated with high acid exposure and delayed reflux clearance in the supine position in GERD patients. Roman et al. showed that large breaks (>5 cm) were associated with incomplete bolus transit (BT) in 100% of cases of GERD, while small breaks (2–5 cm) were associated in only 16% of cases [22]. Large breaks of the peristaltic wave lead to impaired bolus transit and prolonged esophageal acid exposure [25]. In the present study, a significant difference in the median value of the peristalsis break (PB) between the HP-positive and an HP-negative group (3.41±3.65 vs. 6.18±5.27) and the number of PBs >5 cm per 10 swallows (2.23±3.05 vs. 4.04±3.70) between the HP-positive and HP-negative groups, also support that *H. pylori* infection can improve esophageal peristalsis.

Infection with *H. pylori* can stimulate the vagus nerve receptor on the fundus and cardia of the stomach to increase serum gastrin secretion, which can enhance LES pressure, thus protecting the esophageal mucosa and avoiding the esophageal acid exposure. In the present study, the use of HRM, the LES pressure and IRP4s were higher in the HP-positive group compared with the HP-negative group, but the difference was not significant. During esophageal 24-hour pH monitoring, the parameters of the HP-positive group were all lower compared with the HP-negative group (P<0.05). In the HP-positive group compared with the HP-negative group, the composite pH DeMeester scores (9.11±8.15 vs. 24.30±30.27) also indicated a significant difference. The parameters showed that the HP-negative group had a higher esophageal acid exposure.

These findings are in agreement with epidemiological reports that the risk of reflux symptoms and mucosal disease is reduced in *H. pylori*-positive patients. In 20113, Raghunath et al. [10] undertook a systematic review of 20 studies including more than 4,000 patients and found that the odds ratio (OR) for the prevalence of *H. pylori* in GERD patients was 0.60 (95% CI, 0.47–0.78). However, the results differed from previous randomized controlled trials reporting little or no difference in time to relapse between the *H. pylori*-positive and *H. pylori*-negative groups [33]. The present study had a similar design to some previously reported studies, but the important strength of the study was the use of combined HRM with 24-hour pH monitoring analysis, not merely to observe the relationship between *H. pylori* status and GERD, but also to investigate the possible mechanisms of this association.

Conclusions

The findings of this study showed that patients with gastroesophageal reflux disease (GERD) and gastric *Helicobacter*...
pylori (H. pylori) had improved the esophageal peristalsis, enhanced lower esophageal sphincter (LES) pressure, and reduced esophageal acid exposure, indicating a protective effect on the esophageal mucosa from H. pylori. These findings might have implications for future clinical practice, but further research is required to explore the role H. pylori in patients with GERD.

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