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Measurement of gastric pH in ambulatory esophageal pH monitoring

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Abstract
Background Ambulatory esophageal pH monitoring is the method used most widely to quantify gastroesophageal reflux. The degree of gastroesophageal reflux may potentially be underestimated if the resting gastric pH is high. Normal subjects and symptomatic patients undergoing 24-h pH monitoring were studied to determine whether a relationship exists between resting gastric pH and the degree of esophageal acid exposure.
Methods Normal volunteers ($n = 54$) and symptomatic patients without prior gastric surgery and off medication ($n = 1{,}582$) were studied. Gastric pH was measured by advancing the pH catheter into the stomach before positioning the electrode in the esophagus. The normal range of gastric pH was defined from the normal subjects, and the patients then were classified as having either normal gastric pH or hypochlorhydria. Esophageal acid exposure was compared between the two groups.
Results The normal range for gastric pH was 0.3–2.9. The median age of the 1,582 patients was 51 years, and their median gastric pH was 1.7. Abnormal esophageal acid exposure was found in 797 patients (50.3%). Hypochlorhydria (resting gastric pH >2.9) was detected in 176 patients (11%). There was an inverse relationship between gastric pH and esophageal acid exposure ($r = -0.13$). For the patients with positive 24-h pH test results, the major effect of gastric pH was that the hypochlorhydric patients tended to have more reflux in the supine position than those with normal gastric pH.
Conclusion There is an inverse, dose-dependent relationship between gastric pH and esophageal acid exposure. Negative 24-h esophageal pH test results for a patient with hypochlorhydria may prompt a search for nonacid reflux as the explanation for the patient's symptoms.

Keywords Diagnosis · Esophageal pH monitoring · Esophagus · Gastric acid · Gastroesophageal reflux disease · GERD

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Gastroesophageal reflux disease (GERD) is one of the most common diseases in contemporary Western society, and medications for acid suppression are among the most commonly prescribed therapies in the world [1]. The natural history of GERD suggests that pharmacologic therapy is likely to be a lifelong requirement [2]. This emphasizes the importance of making an accurate diagnosis before committing large numbers of patients to long-term therapy with expensive medications.

Endoscopic evaluation is the most commonly used method for determining the diagnosis of GERD in routine practice, but the characteristic appearance of esophageal erosions may be masked by the recent consumption of acid-suppressing medications. In addition, endoscopy cannot address the problem of nonerosive reflux disease (NERD) [3].

For these reasons, direct physiologic measurement of acid in the esophagus by 24-h esophageal pH monitoring remains the gold standard for the diagnosis of GERD.

The accuracy of esophageal pH monitoring in detecting gastroesophageal reflux may be potentially reduced by variations in gastric pH. Little attention has been paid to the status of gastric acid secretion as a potential confounding factor in the interpretation of esophageal pH testing. In particular, the normal range of gastric pH at the time of esophageal testing is not known. The impact of abnormal gastric pH values on the accuracy of esophageal pH monitoring also is unknown.

The current study aimed to establish the normal range of gastric pH at the time of esophageal pH testing and to assess the significance of abnormal gastric pH in the diagnosis of GERD. We performed a retrospective study of normal subjects and symptomatic patients undergoing esophageal 24-h pH monitoring.

Subjects and methods

Normal subject

Asymptomatic volunteers 18–75 years of age with no symptoms of heartburn or dysphagia and no history of esophageal motor disorder or esophageal stricture were recruited. Pregnant subjects and those receiving anticoagulation therapy were excluded. The subjects all had esophageal manometry followed by esophageal pH monitoring and a video esophagogram. All the subjects who had abnormal esophageal acid exposure (pH <4 more than 4.4% of the time) were excluded. The remaining 54 subjects were used to define normal gastric pH.

Symptomatic patients

Patients with symptoms suggestive of GERD referred to the Diagnostic Esophageal Laboratory between October 1998 and January 2007 were studied. A total of 2,266 pH studies were performed. Patients were excluded for the following reasons: no record of gastric pH measurement, pH test shorter than18 h, testing performed while the patient was receiving acid-suppressing medication, previous foregut surgery, or a named motility disorder identified on motility testing.

Esophageal manometry

All drugs interfering with foregut function were discontinued for at least 48 h before the study. After an overnight fast, the manometry catheter was passed through the anesthetized nostril. The catheter had eight water-perfused channels with lateral openings placed 5 cm apart and oriented radially 90° from each other, as previously described [4]. A stationary pull-through technique was used to locate the upper border of the lower esophageal sphincter (LES) for placement of the 24-h pH electrode. Routine examination of esophageal body peristalsis was carried out as previously described [4].

Ambulatory 24-h esophageal pH monitoring

All acid-suppressing medications were discontinued 3 days (H_2-blocking agents) or 14 days (proton pump inhibitors) before the study. Aspirin and nonsteroidal antiinflammatory drugs (NSAIDs) were discontinued 2 days before the study. The subjects attended the esophageal laboratory between 9 am and 12 noon after an overnight fast. The pH catheter with an antimony sensor was calibrated in a standard buffer solution at pH 1 and 7 before and after monitoring. At manometry, the distance from the nares to the upper border on the LES was noted, and a point 5 cm proximal to this level was marked on the pH catheter. The catheter was passed transnasally and advanced into the proximal stomach to record gastric body pH, and then retracted back into the esophagus until the previously marked point appeared at the nares. The catheter was secured to the nose with adhesive tape.

During the study, the subjects and patients were given standardized dietary recommendations and asked not to eat or drink between meals; to avoid carbonated beverages, alcohol, or fruit juices; to remain upright (sitting, standing, or walking) throughout the day; and to lie flat at night for sleep. They were instructed to keep a diary indicating the times of their meals, when they went to bed, when they got up, and when any symptoms occurred.

Esophageal acid exposure was expressed by the standard parameters, namely, percentage of total time the pH was less than 4, time in the upright and supine positions, the number of reflux episodes, the number of reflux episodes lasting longer than 5 min, and the duration of the longest reflux episode. From these six values, a composite pH score (DeMeester score) was calculated using a commercial software program (PolyGram® Net, Medtronic Inc., Minneapolis, MN). The percentage of time that pH was less than 4 during the 2-h period after a regular meal also was recorded.

Data analysis

The 5th and 95th percentile for gastric pH was calculated for the normal subjects. The 95th percentile value was used as the upper limit of normal gastric pH. The patients were

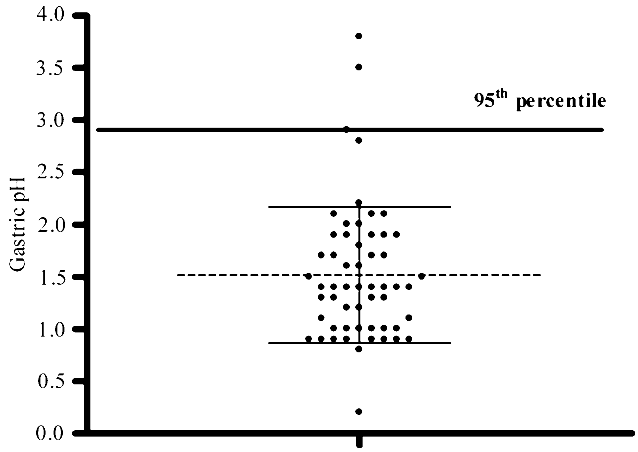

Fig. 1 Gastric pH in 54 normal subjects. Median, interquartile range (IQR) and 95th percentile are shown with lines

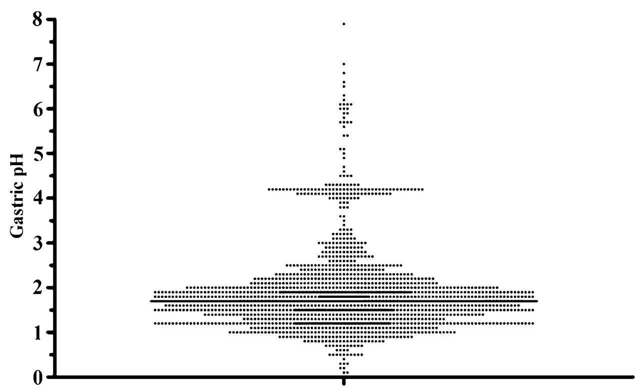

Fig. 2 Gastric pH scatter plot for 1,582 symptomatic subjects showing a bimodal distribution

classified as either normal (gastric pH within the normal range) or hypochlorhydric (gastric pH above the 95th percentile of normal). Esophageal acid exposure was compared between the normal and hypochlorhydric patients. The same analysis then was repeated for a subgroup of patients with abnormal esophageal acid exposure (pH <4 more than 4.4% of the total time).

The patients then were subdivided based on the gastric pH into five categories (pH 0–1, 1–2, 2–3, 3–4, and >4), and the esophageal acid exposure was compared between the groups. Correlation analysis was performed using individual values for gastric pH and esophageal acid exposure in the entire patient population.

Values are reported as median and interquartile range (IQR). The Mann–Whitney *U* test was used to compare continuous variables between the two groups. The Kruskal–Wallis test was used for more than two groups, and the chi-square test was used to assess differences between categorical variables. The Spearman test was used to assess the correlation expressed as the correlation coefficient *R* with 95% confidence intervals (CI). A *p* value less than 0.05 was considered statistically significant. The analysis was performed using Prism 4 statistical software (Graphpad, San Diego, CA, USA).

Results

Normal range

The median gastric pH for the 54 normal subjects was 1.5 (range, 1.1–1.9). The 5th and 95th percentiles were 0.3 and 2.9, respectively (Fig. 1).

Symptomatic patients

Of the 2,266 patients studied, 684 met the criteria for exclusion, leaving a study population of 1,582 patients: 871 women (55%) and 711 men (45%) with a median age of 51 years (range, 41–62 years). The spectrum of the gastric pH in the study population is plotted in Fig. 2. The individual pH values were distributed in a bimodal fashion, with a subgroup of patients having an elevated gastric pH.

Of the 1,582 patients, 1,406 (89%) had a normal gastric pH and 176 (11%) had hypochlorhydria. All the parameters of esophageal acid exposure were significantly higher in those with normal gastric pH, except for the percentage of supine time (Table 1).

In a separate analysis limited to 797 patients with increased esophageal acid exposure on 24-h pH, 720 (90%)

Table 1 Components of the 24-h esophageal pH record in normal gastric pH vs. hypochlorhydria for the total study population

	Normal gastric pH (*n* = 1,406)	Hypochlorhydria (*n* = 176)	*p* Value
% Total time	4.6 (1.3–10.0)	3 (0.3–8.7)	0.0006
% Upright time	5.1 (1.5–11.0)	2.9 (0.3–8.9)	0.0001
% Supine time	0.5 (0–7.2)	0.2 (0–5.15)	0.1921
% Postprandial time	5.9 (1.2–17)	2.5 (0.1–11.0)	0.0001
No. of episodes	63.5 (27.0–122.5)	37 (9.0–90.5)	0.0001
Longest episode (min)	9.4 (3.0–22.0)	7.5 (1.0–21.5)	0.0292
No. of episodes >5 min	2.0 (0.0–5.0)	1 (0–4)	0.0362
Composite pH score	18.3 (6.0–40.0)	11.7 (2.1–34.0)	0.0004

Table 2 Components of the 24-h esophageal pH record in normal gastric pH vs. hypochlorhydria for the patients with proven gastroesophageal reflux disease (GERD)

	Normal gastric pH ($n = 720$)	Hypochlorhydria ($n = 77$)	p Value
% Total time	9.8 (6.7–16)	9.6 (6.7–14)	0.4169
% Upright time	11 (7.1–17)	9.9 (6.3–14)	0.0278
% Supine time	6.6 (0.7–16)	7.8 (1.5–19)	0.4653
% Postprandial time	16 (7.7–27)	11 (3.8–22)	0.0050
No. of episodes	119 (81–185)	104 (68–172)	0.0726
Longest episode (min)	19 (11–36)	22 (14–37)	0.2291
No. of episodes >5 min	5.0 (3–8)	5.0 (3–7)	0.3947
Composite pH score	39.5 (26.0–60.8)	38.4 (25.5–61.2)	0.7344

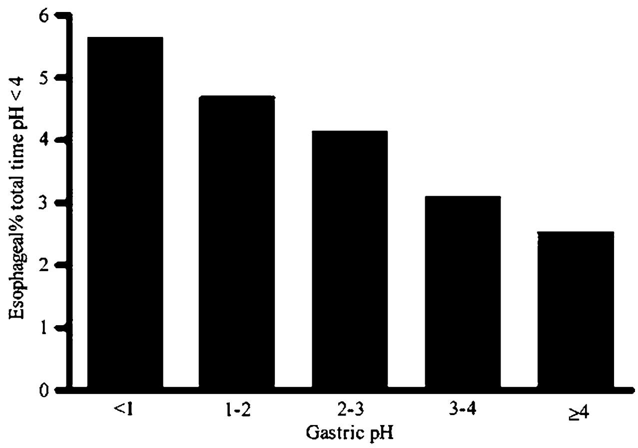

Fig. 3 Percentage of total time pH was lower than 4 across patients with different gastric pH ranges. There is a significant decrease in the percentage of time pH was lower than 4 in groups with higher gastric pH ($p = 0.0002$, Kruskal–Wallis test)

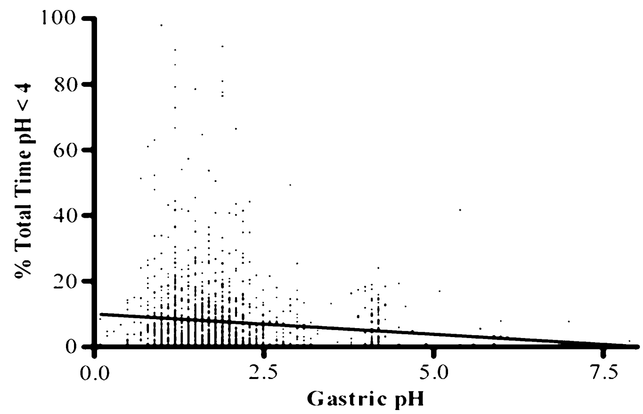

Fig. 4 Correlation between resting gastric pH and percentage of total time pH was lower than 4

Table 3 Esophageal acid exposure (% total time of pH <4) stratified by gastric pH

Gastric pH range	No. of patients	Median % total time pH <4 (IQR)
$\text{pH} < 1.0$	94	5.7 (1.9–12.9)
$1 \leq \text{pH} < 2$	987	4.7 (1.4–10.3)
$2 \leq \text{pH} < 3$	336	4.2 (0.9–9.1)
$3 \leq \text{pH} < 4$	41	3.9 (0.8–6.9)
$\text{pH} \geq 4$	124	2.55 (0.1–8.1)

IQR, interquartile range

had normal gastric pH and 22 (10%) were hypochlorhydric. The patients with hypochlorhydria had paradoxically more supine reflux and more prolonged reflux episodes than the patients with normal gastric pH (Table 2).

The study population was subdivided into five categories based on gastric pH, and the median esophageal acid exposure (percentage of time pH was less than 4) was calculated for each group. A dose-dependent inverse relationship between resting gastric pH and esophageal acid exposure is evident (Fig. 3, Table 3). Figure 4 shows an inverse correlation between the gastric pH and the percentage of time esophageal pH was less than 4 ($r = -0.13$; 95% CI, -0.18 to -0.08; $p < 0.0001$).

Discussion

Over the past three decades, 24-h esophageal pH monitoring has been recognized as the gold standard for measuring esophageal acid exposure [5]. It seems intuitive that the degree of gastric acidity could be a major determinant of esophageal acid exposure. As a result, some authors recommend simultaneous ambulatory gastric and esophageal pH monitoring as a diagnostic approach for patients with GERD [6, 7]. This approach has not been widely adopted in routine practice partly because no consensus exists on how to apply the gastric pH data to the interpretation of the esophageal pH test. It may be argued that the assessment of gastric pH is less meaningful than the measurement of esophageal pH because the latter is based on a prolonged period of observation (minimum, 18 h) rather than on the "dipstick" measurement of gastric pH. However, fasting gastric pH, unlike esophageal pH, is not subject to episodes of abrupt alteration [8]. When assessed in the fasting condition, a one-time spot measurement of gastric pH does appear to have a significant influence on the results of prolonged esophageal pH monitoring.

Previous workers have studied the factors influencing acid secretion of the stomach [9–11]. There is circadian variability in acid secretion, in addition to regional differences within the stomach. Furthermore, total acid secretion, which is dependent on parietal cell mass, also may be affected by gender and by infection with *Helicobacter pylori*. However, although these factors may be valid explanations for variability in gastric pH, they do not affect the relationship between gastric pH and esophageal pH.

The results of the current study confirm that a clear inverse relationship exists between fasting gastric pH and esophageal acid exposure. The higher the gastric pH, the less acid is detected in the esophagus. The relationship is most clearly demonstrated by comparison of the esophageal acid exposure when patients are stratified into groups based on gastric pH. The inverse correlation between esophageal acid exposure and gastric pH is significant but relatively weak. Other factors such as the status of the LES have a greater influence on the degree of esophageal acid exposure [4]. Nevertheless several important observations can be made from this study. Patients with symptoms suggestive of GERD have a gastric pH profile that is bimodally distributed (Fig. 2). Overall, the median pH is slightly higher in patients than in normal subjects (1.7 vs. 1.5), indicating that GERD is not primarily a hypersecretory disease.

Patients with elevated gastric pH may have GERD undetected by 24-h esophageal pH testing [12, 13]. Indeed, patients with hypochlorhydria, as defined by a gastric pH exceeding the 95th percentile of normal, had less esophageal acid exposure than those with gastric pH in the normal range. Among the 797 patients who had abnormal 24-h esophageal pH test results, those who were hypochlorhydric actually had a greater supine acid exposure, and the longest reflux episode was of greater duration. This suggests that hypochlorhydric patients may have increased esophageal acid exposure despite weaker gastric acidity due to poor esophageal clearance of the refluxed acid.

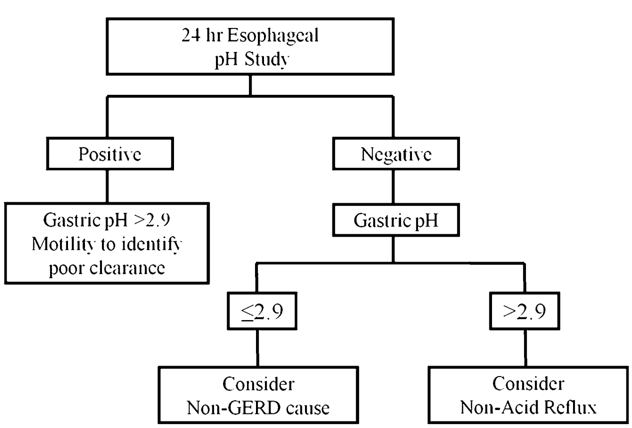

Fig. 5 Suggested algorithm for interpreting 24-h esophageal pH monitoring by considering gastric pH

Based on the outcome of this study, we propose a simple algorithm to guide physicians in their interpretation of esophageal pH testing in the light of the gastric pH (Fig. 5). When the 24-h pH test results show abnormal esophageal acid exposure, the diagnosis of GERD is clear. The only importance of an elevated gastric pH in these patients is to prompt further study of esophageal clearance by esophageal manometry.

However, for patients with normal 24-h esophageal pH test results, the presence of hypochlorhydria suggests that the symptoms may be caused by nonacid reflux. These patients would benefit from multilevel intraluminal impedance (MII) to detect nonacid clearance. In contrast, a normal 24-h esophageal pH study for a patient with a normal gastric pH is more likely to be a true negative. Such patients should be evaluated for other causes of their symptoms.

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