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ORIGINAL ARTICLE

# Dual Ambulatory pH Monitoring in Patients with Gastroesophageal Reflux Rendered Asymptomatic with Proton Pump Inhibitor Therapy

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**Abstract**
*Background* Studies have suggested that proton pump inhibitor (PPI) therapy in gastroesophageal reflux disease (GERD) achieves high rates of esophageal acid normalization.
*Aims* Our aims were to investigate the adequacy of esophageal and gastric acid suppression in reflux patients rendered asymptomatic on optimized PPI therapy.
*Methods* We retrospectively analyzed outcomes of dual-sensor, ambulatory 24-h pH monitoring in referred persistent reflux patients rendered asymptomatic on PPI therapy. After optimization, we analyzed esophageal and gastric pH profiles to assess acid suppression and examine differences between PPIs. In patients with repeat studies, comparisons between different PPI doses were made.
*Results* Of 172 asymptomatic GERD patients, 75 (43.6 %) achieved symptomatic remission with once-daily dosing PPI, and 97 (56.4 %) patients required twice-daily dosing. Of the entire cohort, 93 (54.1 %) had abnormal and 79 (45.9 %) had normal esophageal pH profiles, with mean percent time pH $< 4.0$ of 14.3 and 2.4, respectively ($p < 0.0001$). The percent time esophageal pH was abnormal did not correlate with the percent time gastric pH was abnormal ($p = 0.17$). Different PPI formulations demonstrated differences in gastric—not esophageal—pH times, with esomeprazole exhibiting superior gastric pH suppression ($p < 0.0001$). Overall, gastric pH control remained suboptimal, with pH $< 4.0$ ranging between 30 and 50 %. Among patients with sequential pH studies, those with higher PPI dose had improved esophageal pH profiles ($p < 0.01$).
*Conclusions* In GERD patients rendered asymptomatic on PPI therapy, most continue to experience abnormal esophageal and gastric acid exposure. The efficacy of acid suppression therapy, in certain patients, may be much lower than previously thought.

**Keywords** GERD · PPI · Acid suppression · Ambulatory pH monitoring · Gastric pH · Esophageal pH

**Abbreviations**

| | |
|---|---|
| GERD | Gastroesophageal reflux disease |
| PPI | Proton pump inhibitor |

## Introduction

Gastroesophageal reflux disease (GERD) is widely prevalent, afflicting up to 20 % of the population [1], and has significant implications on healthcare costs with annual expenditures of up to 10 billion dollars [2]. Although many patients can be simply diagnosed by typical symptoms and response to empiric proton pump inhibitor (PPI) therapy, in a subset of patients, additional diagnostic and postthera-peutic testing is indicated. Refractory GERD is also increasingly prevalent, seen in up to 45 % of patients placed on empiric PPI therapy [3], and often results from noncompliance, misdiagnosis, or poor esophageal pH control. Recent practice guidelines suggest that ambulatory pH monitoring is particularly useful in endoscopy-negative patients with typical reflux symptoms refractory to PPI therapy [4].

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Ambulatory pH monitoring is contextually implemented and interpreted with the assumption that patients on PPI therapy achieve high rates of normalization of esophageal acid exposure resulting in turn from gastric acid suppression. However, there are limited data with pH monitoring performed in asymptomatic patients on PPI therapy [5, 6]. Although a Veterans Affairs (VA) study reported that asymptomatic patients on acid suppressive therapy have a significant proportion of residual pathological acid reflux [5], this has not been reproduced in other cohorts [7–9]. Several important questions remain unanswered: What percentage of GERD patients rendered asymptomatic on PPI still suffers from pathologic esophageal acid reflux? What is the magnitude of gastric acid suppression accomplished by PPI? Are there any differences among the various PPI agents in their potential to control esophageal and gastric pH? Is acid suppression dose-dependent?

The aims of this study were to investigate esophageal and gastric acid suppression in a community cohort of GERD patients rendered asymptomatic on optimized PPI therapy and attempt to answer these questions.

## Methods

The study was approved by the Institutional Research Board of El Camino Hospital and was conducted at the Neurogastroenterology and Motility Center in Mountain View, CA. All patients gave written consent prior to the pH monitoring studies. Because all the data were collected by reviewing existing records, the study was exempted from the need for individual informed consent from participating patients.

We studied patients with nonerosive and erosive reflux disease, including Barrett's esophagus, who were all initially evaluated because of persistent heartburn, acid regurgitation, or both. Upon their initial presentation, all patients in the cohort had heartburn and acid regurgitation as the predominant symptoms. Dysphagia and chest pain were not the main presenting complaints, and they were elicited on subsequent questioning and formal questionnaire analysis. Patients with atypical (ENT or respiratory) symptoms were not included in this study. A review of patient's medical, endoscopic, motility, and histological records was then performed to ensure qualification in the study.

Patients were classified in various disease categories as follows: nonerosive reflux disease (NERD): endoscopy-negative but abnormal pH scores off PPI; erosive reflux disease (ERD): endoscopy-positive for any LA classification grades; Barrett's esophagus: endoscopically visible and histologically proven intestinal metaplasia. Endoscopy was performed at the time of referral while patients were on PPI therapy, and prior to PPI optimization. Patients, who had been found to be *Helicobacter pylori* (*H. pylori*) positive by either antral biopsies or urease testing during initial endoscopy, were first treated and then reassessed symptomatically after eradication, prior to inclusion in the study. We excluded patients who had previously undergone esophageal or gastric surgery in order to avoid the impact of any potential functional or structural alterations that such surgeries would impose. In order to qualify for inclusion into the study, patients had to be asymptomatic, confirmed by having a total score of 0 on a simple and previously used GERD questionnaire while on optimized PPI therapy [10]. In this questionnaire, the symptoms were graded with scores for heartburn, regurgitation, chest pain, dysphagia (0 = no symptom, 1 = mild symptom, 2 = moderate symptom, and 3 = severe symptom), nighttime symptoms (0 = no, 2 = yes), and symptom frequencies (once a week = 0, 2 to 6 times a week = 1, 7 to 15 times a week = 2, and more than 15 times a week = 3). The time frame of symptoms assessed in the survey was less than 1 month.

All participating patients were optimized to symptom resolution on PPI therapy, by optimizing the frequency, timing, and dose or type of PPI. If patients persisted experiencing nocturnal symptoms while on once-daily PPI, the frequency of PPI was increased to twice daily, with a single-standard dose given at night. Furthermore, if the patient persisted having daytime symptoms on a single-standard morning dose, double the standard dose was prescribed in the morning. All commercially available agents were used as directed by patients' choice, insurance coverage, and tolerability. PPI therapy was taken 30 min before breakfast and, in the case of twice-daily dosing, before dinner as well, for at least 2 weeks prior to the dual-channel 24-h ambulatory pH monitoring. Symptom resolution was ensured using GERD questionnaire score of 0, based on typical reflux symptoms, nightly symptoms, and frequency of symptoms (see above). Some patients who failed to control esophageal pH agreed to undergo sequential pH monitoring on higher PPI dosage and were analyzed separately.

### Dual-Channel 24-Hour Ambulatory pH Monitoring

Ambulatory pH monitoring was performed while on PPI therapy using a dual-sensor pH catheter connected to a portable digital data recorder (Digitrapper pH 400, Synectics Medical Ltd.) that stored data for up to 24 h. The positioning of the catheter was established using the pull-through technique, utilizing the pH difference between the distal (gastric) and proximal (esophageal) sensors and previous LES identification by esophageal motility. The operator advanced the probe while the patient was drinking

water until the pH dropped below 4; then, the catheter was pulled back 5 cm above the superior border of the LES, based on previous high-resolution esophageal manometry. The catheter's distal sensor recorded pH 10 cm below the gastro-esophageal junction, and its proximal sensor recorded 5 cm above the lower esophageal sphincter. In addition to pH, symptoms, body position, and mealtime data were manually recorded. Patients were instructed to carry out normal daily activities without dietary restrictions. No instructions were given in regards to consumption of food or drink between dinner and bedtime. To ensure PPI compliance, for all patients, verbal confirmation was obtained of continuous PPI therapy 5 days prior to pH study, including before breakfast on the day of the study. Failure to do so resulted in rescheduling of ambulatory pH monitoring. Patients were reminded to take PPI 30 min prior to meal(s) based on their scheduled dosing regimens.

The pH data were analyzed using standard software (Polygram Net, Synectics Medical Ltd.). A reflux episode was defined as a drop in pH in the distal esophagus or stomach below 4.0. The pH profile included the percent of total time with pH less than 4.0 and analyzed separately by patient position, in both the esophageal and gastric sensor. We defined an abnormal esophageal pH profile as greater than 5 % of the total time with esophageal pH $< 4$. The 5 % cutoff was determined based on previous pH studies and consensus guidelines [7, 8, 11]. Given the lack of consensus for abnormal gastric pH profiles, the percent time gastric pH $< 4$ was reported for patients. In patients with multiple ambulatory pH studies, only the one performed on the highest dose of PPI therapy was analyzed.

### Statistical Analysis

Statistical analysis was performed using GraphPad Prism 6 software (La Jolla, CA). The percentages of time with pH $< 4.0$ in the distal esophagus and the stomach were analyzed separately for total, upright, and supine periods. For the distal esophageal sensor recordings, the DeMeester scoring system was utilized. The components of a positive score require a percentage total time that the pH $< 4.0$ of 5.5 % or greater, percentage upright pH $< 4.0$ of at least 8.2 %, percentage supine pH $< 4.0$ of 3 % or more, and more than 99 reflux episodes per 24 h. A reflux episode was defined as a drop in pH in the distal esophagus or the stomach below 4.0. The duration of each reflux episode was measured from the time that the pH dropped below 4.0 to the time that the pH returned to a level above 4.0. With patients having multiple pH studies, only those with the highest dose of PPI therapy was included for analysis.

The 2-tailed $t$ test was used to compare continuous variables. Linear regression analysis was used to correlate esophageal and gastric pH levels. Further analysis was performed in the subset of patients with repeated pH monitoring. Only studies performed with escalating doses of the same PPI were included for analysis, whereas those with different PPI therapy were excluded. For all statistical analysis, the level of significance was set at $p < 0.05$.

**Table 1** Patient demographics and characteristics

| | |
|---|---|
| Number of patients | 172 |
| Mean age | 56 |
| Gender (M:F) | 87:85 |
| Mean time (min) esophageal pH $< 4$ [CI] | |
| Upright | 84 [70, 98] |
| Supine | 48 [36, 59] |
| Mean number of reflux events [CI] | |
| Upright | 144 [124, 164] |
| Supine | 70 [56, 83] |
| Mean % time pH $< 4$ [CI] | |
| Esophageal | 9.1 [7.6, 10.6] |
| Gastric | 42 [36.4, 48.5] |
| Number (%) total time >5 % w/ pH $< 4$ | 93 (54.1 %) |

## Results

One hundred and seventy-two patients who had initially presented with persistent heartburn and regurgitation and eventually had been rendered asymptomatic after PPI therapy were studied. The cohort had a mean age of 56 with even distribution between genders (Table 1). All 6 commercially available PPI therapies were represented. The cohort was primarily patients with NERD ($n = 110$, 64.0 %), followed by those with erosive disease ($n = 17$, 9.9 %) and, finally, with a significant portion of patients with Barrett's esophagus ($n = 45$, 26.1 %). On the average, patients were bi-positional refluxers, with greater acid exposure during the upright as opposed to the supine positions.

Of these 172 patients, 75 (43.6 %) had achieved symptomatic remission with a once-daily dosing PPI regimen, and 97 (56.4 %) patients had required twice-daily dosing (Fig. 1; Table 2). Of the latter group, 15 (15.5 %) patients required standard dose given twice daily and 82 (84.5 %) patients required double-standard dose in the morning in addition to single-standard dose in the evening. Those with continued abnormal pH studies, defined as greater than 5 % of total time with esophageal pH $< 4$, accounted for the majority of patients in both the once-daily ($n = 40$) and twice-daily ($n = 53$) groups. Of the entire cohort, 79 (45.9 %) had normal and 93 (54.1 %) had abnormal esophageal pH profiles, with mean % time of 2.4 and 14.3, respectively ($p < .0001$). We found no

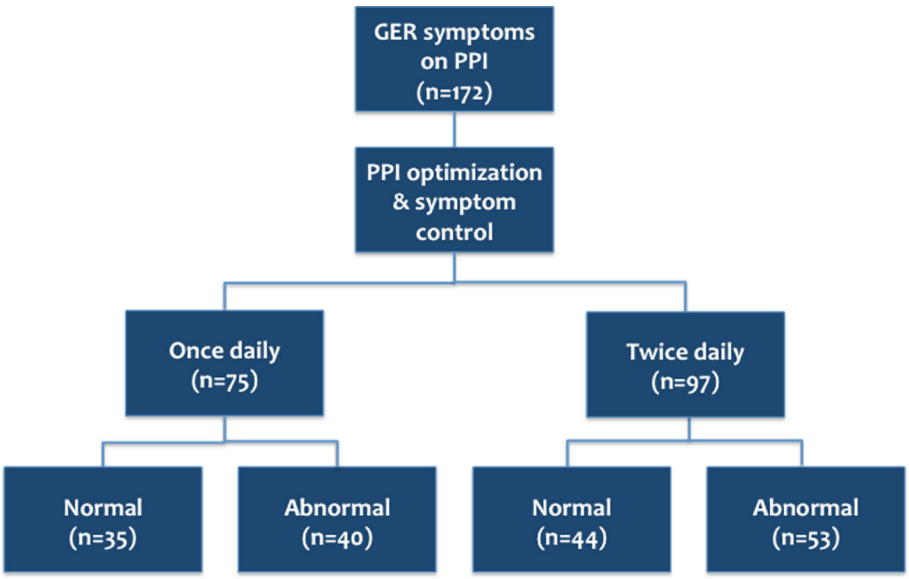


**Fig. 1** Flow diagram illustrating medically optimized, symptomatic GER patients, grouped by PPI dosing regimen, with significant proportion of abnormal pH studies

**Table 2** Esophageal and gastric pH control with once- or twice-daily PPI therapy

| | Daily ($n = 75$) | | | BID ($n = 97$) | | |
|---|---|---|---|---|---|---|
| | Normal | Abnormal | $p$ value | Normal | Abnormal | $p$ value |
| $n$ | 35 | 40 | | 44 | 53 | |
| % Esophageal pH < 4 | 2.57 | 13.62 | <.0001 | 2.46 | 15.62 | <.0001 |
| % Gastric pH < 4 | 46.27 | 52.56 | 0.25 | 34.39 | 37.83 | 0.48 |

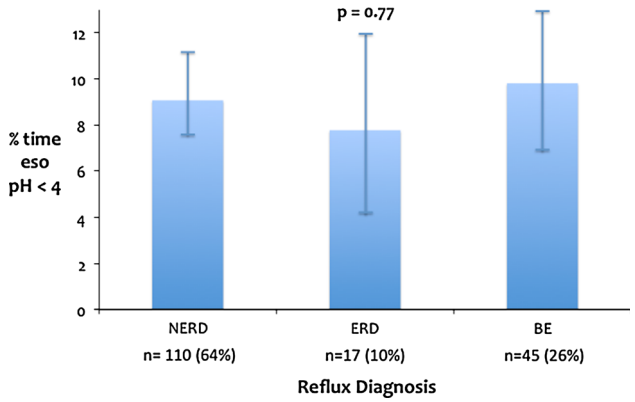


**Fig. 2** Comparison of mean percent times (with associated confidence intervals) of esophageal pH < 4.0 in patients with nonerosive reflux disease, erosive reflux disease, and Barrett's esophagus

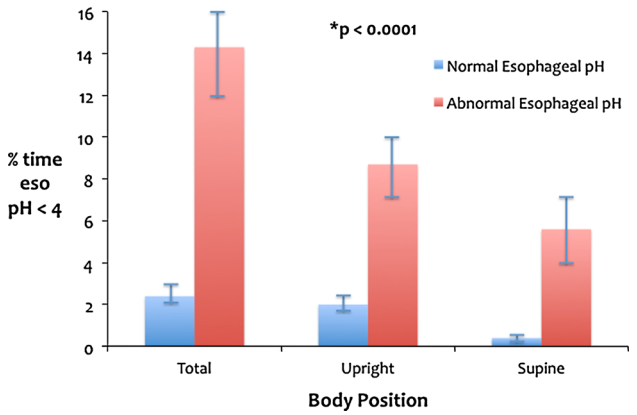


**Fig. 3** Comparison of mean percent times (with associated confidence intervals) of esophageal pH < 4.0 in patients with normal and abnormal pH profiles, grouped by body position

differences in esophageal pH control between patients with NERD, ERD, and Barrett's esophagus ($p = 0.77$) (Fig. 2). The mean % time with gastric pH < 4 was 42 %, despite optimized PPI therapy. We then analyzed the percent time esophageal pH was abnormal (less than 4.0) based on the patient being upright or supine. Regardless of body positioning, those with abnormal pH studies had significantly lower time with pH < 4 compared with those with normal pH studies (all $p < 0.0001$) (Fig. 3). There were no differences in age, gender, or PPI dose between patients with normal and abnormal esophageal pH scores (data not shown).

We then examined the relationship between gastric and esophageal acid suppression with PPI therapy. The percent time esophageal pH was abnormal (pH < 4.0) did not correlate with the percent time gastric pH was abnormal

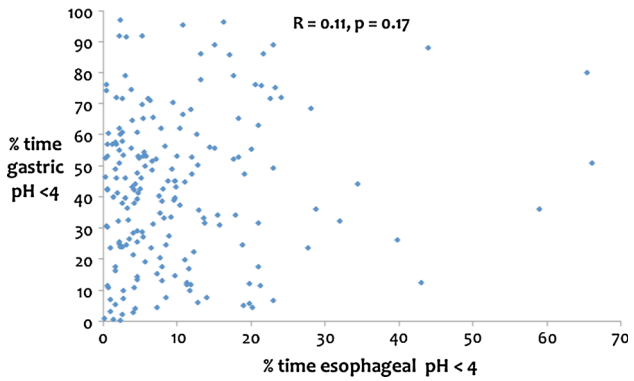


**Fig. 4** Relationship between percent times with esophageal and gastric pH < 4.0 while on PPI therapy ($R^2 = 0.011$, $p = 0.1681$)

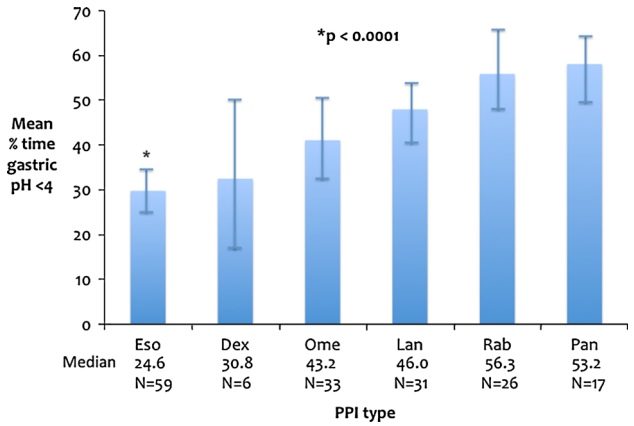


**Fig. 5** Comparison of mean percent times (with associated confidence intervals) of gastric pH < 4.0 in patients receiving different types of PPI therapies

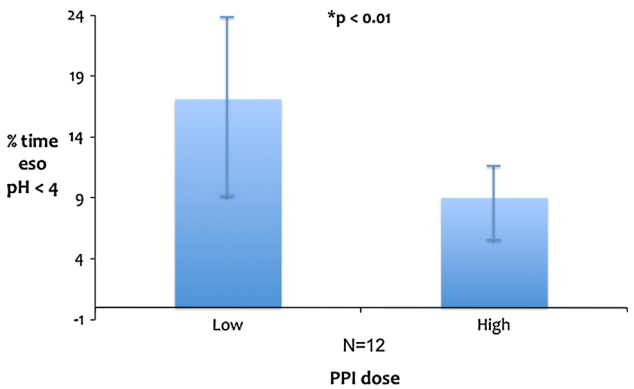


**Fig. 6** Comparison of esophageal pH profiles of low- and high-dose PPI therapies

($r = 0.11$, $r^2 = 0.011$, $p = 0.17$) (Fig. 4). The type of PPI therapy had no effect on esophageal pH profiles. However, different PPI formulations did demonstrate differences in the mean % time with gastric pH < 4.0; such analysis revealed that esomeprazole had superior gastric pH suppression ($p < .0001$) (Fig. 5). Overall, gastric pH control remained suboptimal, with mean gastric pH < 4.0 values ranging between 30 and 50 %.

Finally, among the 12 patients with sequential ambulatory pH studies, we examined the effect of incremental increases in daily PPI dose on esophageal acid suppression. Those with higher PPI dose had significantly improved esophageal pH times <4 ($p < 0.01$) (Fig. 6).

## Discussion

The aim of this study was to investigate acid suppression in GERD patients presenting with typical persistent reflux symptoms despite PPI but eventually rendered asymptomatic after therapy optimization with once- or twice-daily PPI therapy. We have demonstrated that the majority of such patients, despite being asymptomatic on optimized PPI therapy, had poor esophageal acid control and ongoing gastric acidity. These results question the importance of esophageal pH normalization in symptom control and potentially invalidate pH monitoring as a useful clinical endpoint in GERD clinical trials.

To date, there have been limited and controversial data on the normalization of esophageal acid exposure while on PPI therapy. Several studies have suggested PPI therapy is associated with high rates of acid normalization [7–9]. In one single-center, double-blind, randomized, two-way crossover study of 20 patients who were treated for two 7-day periods separated by a washout period, continued esophageal acid reflux was only seen in up to 15 % with a once-daily regimen [7]. In another retrospective review of 250 pH tracings of symptomatic patients on optimized, twice-daily PPI therapy, those with typical reflux had abnormal esophageal pH studies in 7 % [8]. Furthermore, even in studies with much stricter criteria used to define acid normalization, for example, with esophageal pH < 4 less than 1.6 % of the time, the majority of patients (69 %) on PPI therapy had normal studies [9]. In contrast, a VA study by Milkes et al. [5] demonstrated abnormal esophageal pH in 50 % of GERD patients despite optimized PPI therapy achieving complete symptom control. Notable limitations of that study included a relatively small sample size and the nongeneralizability of a veteran population, primarily comprising Caucasian males with significant comorbidities. Furthermore, VA population studies have demonstrated low rates of medication compliance with PPI therapy [12]. In another prospective, single-center study, one-third of unselected patients with GERD rendered asymptomatic on PPIs had increased esophageal acid exposure, especially if their PPI was administered once

daily [6]. Our current study not only confirms low rates of esophageal acid normalization while on PPI therapy, but it also utilizes a large cohort of males and females in a community setting with good generalizability to the larger population of PPI users.

Some argue that ambulatory pH monitoring on PPI therapy has low yield given the high rates of acid normalization and suggests other diagnostic modalities, including impedance-pH monitoring, to account for nonacid reflux. Studies have shown that while on PPI therapy, despite a decrease in acid reflux, there has been a concurrent increase in nonacid reflux or weakly acidic reflux, with significant symptom correlation [13, 14]. Our study did not involve impedance measurements but clearly demonstrated a significant proportion of patients with abnormal pH studies despite PPI therapy, suggesting that the potential yield of pH monitoring alone may be higher than previously thought.

Studies have suggested that patients with asymptomatic Barrett's esophagus on daily and twice-daily PPI therapy have high rates of abnormal acid exposures, at 60 and 24 %, respectively [15]. As a referral center for reflux disease and Barrett's esophagus, our study site had a significant proportion of Barrett's esophagus (26 %), and further analysis revealed that these patients had comparable esophageal pH profiles to that of NERD and ERD patients in our cohort. The absence of differences seen in esophageal pH between NERD, ERD, and Barrett's esophagus may be attributable to the fact that endoscopy was performed while on PPI therapy. Many NERD patients could have been ERD patients prior to endoscopy and institution of PPI therapy.

With PPI therapy, we may have also underestimated the number of EE patients, which may explain why we did not see more acid reflux in EE patients.

We were unable to demonstrate a correlation between esophageal and gastric pH in our PPI-treated patients. When Milkes et al. [5] examined the possible predictors of persistent acid GER, they found a significant relationship between residual gastric acidity and the amount of esophageal acid exposure, whereas the presence of hiatus hernia, ineffective esophageal peristalsis, and/or lower esophageal sphincter were not relevant. However, our findings seem to confirm that of smaller prospective studies investigating nocturnal acid breakthrough, which suggest that with PPI therapy, gastric pH was much more difficult to control than esophageal pH [16, 17].

Interestingly, in our current study, there was superior gastric acid suppression on esomeprazole than with other agents. In a randomized, open-label, comparative five-way PPI crossover study, esomeprazole provided a significantly higher percentage of gastric pH greater than 4.0 for more than 12 h relative to the other PPIs [18]. A meta-analysis of esomeprazole versus alternative PPIs demonstrated a modest benefit in healing and symptom relief in patients with erosive esophagitis [19]. However, only limited data are available to suggest an association between gastric acidity and esophagitis healing [20]. In the current study, there was suboptimal gastric acid inhibition using PPI therapy. However, conclusions drawn from gastric pH monitoring are difficult to interpret, as drawbacks include inability to factor the volume of acidic contents, interactions with ingested food, and compartmentalization of gastric contents [15]. Our current corroborative gastric pH results dispel the notion that clinically significant gastric hypochlorhydria is induced by PPI therapy, raising doubts as to possible downstream pH-related adverse side effects.

There are some notable limitations to the current study. First, this cohort is a select population who were willing to undergo pH monitoring and aggressive acid suppressive therapy to exclude residual acid reflux, and as a group, they represent a small fraction of those evaluated at our center. Although all patients in the cohort were successfully rendered asymptomatic, they initially presented with persistent symptoms and represent a tertiary referral group. However, half of these patients were rendered asymptomatic on once-daily dosing therapy by simply changing the timing, dose, or type of PPI. Our symptom questionnaire ensured that patients did not have typical reflux symptoms; however, some patients had belching, bloating, or dyspepsia, motivating some to undergo further pH studies. Our study was driven by practical questions raised by our patient population. Specifically, patients were concerned about subclinical esophageal acid exposure and malignancy, as well as PPI effects on gastric acid and calcium absorption, fractures, etc; thus, they wanted esophageal pH normalization to the best degree possible. Second, although efforts were made to ensure compliance on PPI therapy, our study did not utilize direct observed therapy or pill counting for further confirmation. Third, patients in the study did not have fixed dosing regimens or medications, standardized meals, or long-term follow-up. The different doses of PPI therapy may have confounded our findings, in particular, suggesting that esomeprazole exhibited superior gastric pH control. Regarding the lack of explicit PPI regimen standardization, one may interpret our results in the context of a real-life, community-based study. We were able to demonstrate poor acid control with all PPIs represented and in all presentations of reflux disease. Fourth, the current study utilized 24 h dual catheter, which may be limited by patient tolerability and inability to record periods beyond 24 h, including periods off and on PPI therapy during the same study. Finally, the retrospective nature of the study limits the strength of the associations described, and prospective studies are needed to confirm these observations. Nevertheless, we were able to demonstrate robust results in

a large cohort of asymptomatic GERD patients with good generalizability.

*In summary*, in GER patients rendered asymptomatic on PPI therapy, there exists a significant proportion of abnormal ongoing esophageal and gastric acid exposure. This effect applies to NERD, ERD, and Barrett's esophagus. The efficacy of acid suppression therapy, in certain patient populations, may be much lower than previously thought. In asymptomatic patients with pathological acid reflux, the management and implications are still unclear.

**Conflict of interest** The authors declare that they have no conflict of interest to disclose.

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