

Donald O. Castell, M.D., Series Editor

## Circadian Reflux Pattern on PPI Therapy



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### Background and Aims:

The normal circadian pattern of intragastric acidity is an increase in acid secretion beginning in the evening until midnight. The circadian pattern for esophageal reflux is largely unknown. Combined impedance-pH monitoring (MII-pH) has the ability to detect both acid and non-acid reflux episodes, and thus to clarify on-going reflux throughout the day, including during post-prandial buffering and pharmacologic altering of gastric content. The aim of this study was to analyze the circadian pattern of both acid and non-acid reflux and the effect of PPI therapy.

### Methods:

A retrospective review was performed on 300 patients. All had undergone ambulatory MII-pH studies. Patients were selected by therapeutic regimen with 100 patients on PPI twice a day, 100 patients on PPI once a day, and 100 patients off PPI. We assessed the total number of reflux episodes per hour, the number of acid and non-acid reflux episodes per hour, and plotted the hourly distribution of the circadian pattern from 0600-0600. Reflux episodes were evaluated separately for upright and recumbent positions. Approval for retrospective chart review was obtained from the Institutional Review Board (IRB) of the Medical University of South Carolina. The comparison of the 3 groups was performed using ANOVA.

### Results:

300 patients were selected (162 females) with mean age of 56 years (18-84). The mean number of reflux episodes per day per patient was 24.3 in the off PPI group, 32.00 in the QD PPI group and 28.2 in the BID PPI group. The mean number of acid episodes per day per patient was 15.6 in the off PPI group, 6.2 in the QD PPI group and 5.1 in the BID PPI group. The mean number of non-acid episodes per day per patient was 8.7 in the off PPI group, 25.8 in the QD PPI group and 23.1 in the BID PPI group.

### Conclusion:

Our study showed various findings. Among the most important is that the frequency of the circadian patterns of all types of reflux (acid and non-acid) is similar both on and off PPI therapy. Only the pH of the refluxate is significantly affected by PPI therapy.

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## INTRODUCTION

**G**astroesophageal reflux disease (GERD) is a common entity, affecting approximately one third of the US population at least once a month and 7% on a daily basis.<sup>1</sup> The presenting symptoms associated with GERD vary from the more typical heartburn and regurgitation to extraesophageal symptoms such as cough and throat clearing. Proton pump inhibitor (PPI) therapy has become the standard treatment for patients with GERD.<sup>2</sup>

The normal circadian rhythm of intragastric acidity is usually an increase in the acid secretion in the evening until the middle of the night and then a decrease in the morning.<sup>3</sup> The circadian rhythm for total esophageal reflux episodes is unknown. Gudmundsson<sup>4</sup> in 1988 showed that the time pattern of GERD separated into 3 periods when studied with ambulatory 24 hour esophageal pH-monitoring and identified the most acid reflux episodes in the evening.

Ambulatory Impedance-pH technology (Imp-pH) provides the opportunity to monitor all reflux episodes; acid and non-acid in type, both in the upright and recumbent positions.<sup>5,6</sup> This test avoids a false positive study due to acidic meals or drinks and is becoming the gold standard for detection and analysis of GERD and for clarifying its relationship to symptoms.<sup>7,8</sup> Excluding the meal periods from ambulatory pH monitoring improves the diagnosis of esophageal reflux disease.<sup>9</sup> The goal of this study was to further characterize the daily pattern of reflux and the effect of PPI therapy on it using combined pH and impedance to identify all types of reflux.

## MATERIALS AND METHODS

A retrospective review was performed on MII-pH studies from 300 patients (162 females); age range 18-84 years,

**Table 1. Mean 24 Hour Reflux Episodes Per Patient**

	PPI BID	PPI QD	PPI OFF
<b>Total episodes</b>	28.2	32.0	24.3
<b>Non-acid episodes</b>	23.1	25.8	8.7
<b>Acid episodes</b>	5.1	6.2	15.6

who underwent testing to evaluate symptoms felt to be possibly due to GERD. These MII-pH studies were performed on 100 patients each on twice a day (BID) PPI therapy, once a day (QD) PPI therapy and off (OFF) PPI therapy. The Imp-pH studies were performed from February 2006 until February 2008.

Indications for the test were heartburn, regurgitation, indigestion, persistent cough, asthma or throat clearing.

## Exclusion Criteria:

- Patients on more than one reflux therapy agent (H2 blockers, more than 1 PPI, baclofen, sucralfate)
- Studies with only upright or only recumbent readings.
- History of a previous Nissen fundoplication.

A standard multichannel intraluminal impedance pH (Imp-pH) catheter (*Sandhill Scientific Inc., Highlands Ranch, CO*) was used. This 2mm diameter catheter has the ability to record esophageal and gastric pH, along with the presence and direction of any liquid flow in the esophagus. The MII-pH catheter was passed through the nasal cavity and into the stomach in the morning 0800-1000 in fasting patients. The catheter was slowly pulled back in a stepwise fashion to locate the LES using the single pressure sensor in the distal portion of the catheter. Dual pH monitoring was located at 5 cm above and 15 cm below the proximal margin of the LES with 6 impedance sensors at 3, 5, 7,9,15 and 17 cm above the LES.

## The following parameters were assessed:

- Total number of reflux episodes (acid and non-acid) per hour (both upright and recumbent)
- Type of reflux; acid or non-acid.
- Relation of reflux episodes to the beginning of the recumbent time.

The daily analysis was further divided into 3 segments: morning between 0600- 1400, evening between 1400-2200, and night between 2200-0600. Meal times indicated by the patient on MII-pH studies were excluded from data analysis. Comparison of the 3 groups was performed using ANOVA.

## RESULTS

The mean number of daily reflux episodes per patient off PPI was 24.3, on QD PPI it was 32.00 and on BID PPI it was 28.2 (Table 1). These were not significantly (NS) different, although interestingly numerically greater in the two groups studied on PPI. The mean number of acid reflux episodes per patient was 15.6 off PPI. It was 6.2 on QD PPI and 5.1 on BID PPI ( $p < 0.05$ ). The mean number of non-acid reflux episodes per patient in off PPI was 8.7, on QD PPI it was 25.8 and on BID PPI was 23.1 ( $p < 0.05$ ). There was also no significant difference between total number nor type of reflux seen on PPI therapy comparing QD with BID.

The circadian patterns of reflux episodes in the three patient groups were similar. (Fig. 1-3) The circadian pattern of the off PPI group (Figure 1) is similar to that of the QD PPI group (Figure 2), with peaks around meal and postprandial hours and a drop in the number of episodes after 11pm. The circadian pattern in the BID PPI group (Figure 3) is similar to those of the off PPI and QD PPI groups. There is an increase in the average reflux episodes per hour around lunch time which continuously increases with peaks around 2pm and 7pm related to the post prandial state. Reflux episodes were frequent in the evening postprandial period. There is a sudden drop in the number of reflux episodes after 11pm. During night time recumbency there were less frequent reflux episodes with no significant difference between the OFF and ON therapy groups ( $< 1$  episode/hour in all groups).

Figure 4 (a,b,c) shows the decrease in the average number of reflux episodes when assuming the recumbent position, shown with episodes aligned to the start of recumbency (R) for all 3 groups.

The total number of reflux episodes seen in the 3 groups was 8455 (Figure 5). Of these, only 862 (10.2%) occurred in the recumbent position. In the off PPI group, 11.0% of the episodes were seen in the recumbent position. In the QD PPI group it was 10.3% and in the BID PPI group it was 9.4% of the total episodes (NS)

When analyzing the mean reflux episodes per hour during each segment of the day, most of the episodes (nearly double) were seen in the evening when compared to the other two segments of the day. (Figure 6) The mean number of reflux episodes in the evening in the off PPI group was 1.9 and was 2.6 and 2.3 in the QD and BID PPI group respectively. These values are not significantly different. Also, there was no significant difference between the mean reflux episodes in the

Figure 1. Circadian Pattern of Reflux Episodes OFF PPI

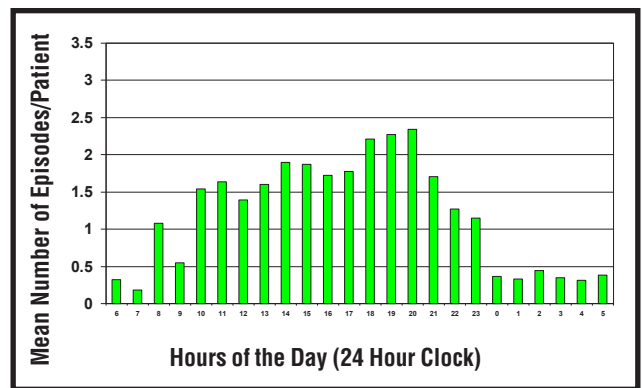


Figure 2. Circadian Pattern of Reflux Episodes on QD PPI

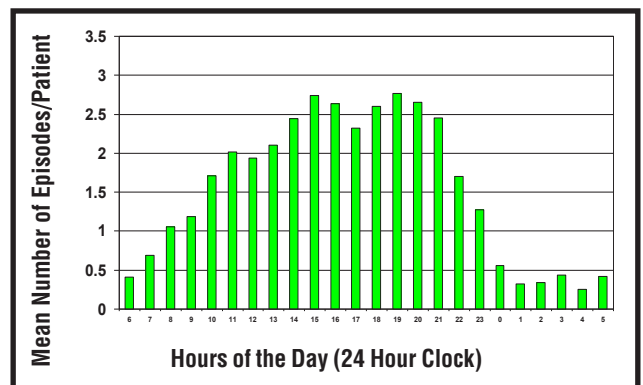
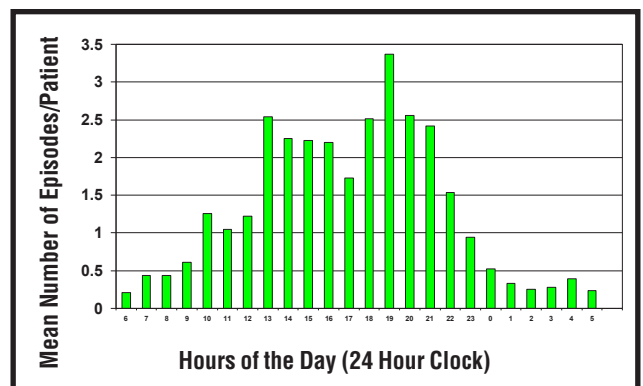


Figure 3. Circadian Pattern of Reflux Episodes on BID PPI



morning. Mean reflux episodes was 1.0 in the off PPI group, 1.3 in the QD PPI group and 0.9 in the BID PPI group. During the night time, mean number of reflux episodes was 0.6 in the off PPI group, 0.7 in the QD PPI group and 0.5 in the BID PPI group (NS).

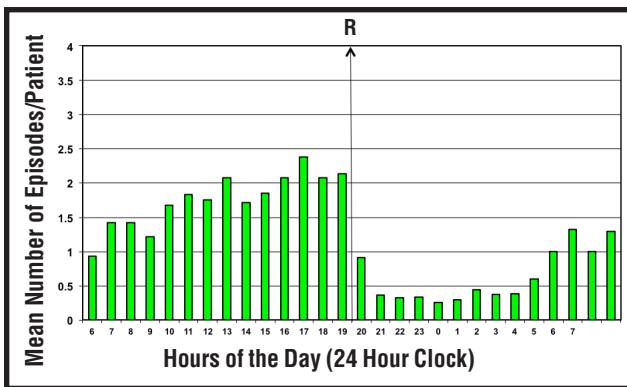
As expected, when the total reflux episodes were divided into acid and non-acid in type in the off PPI

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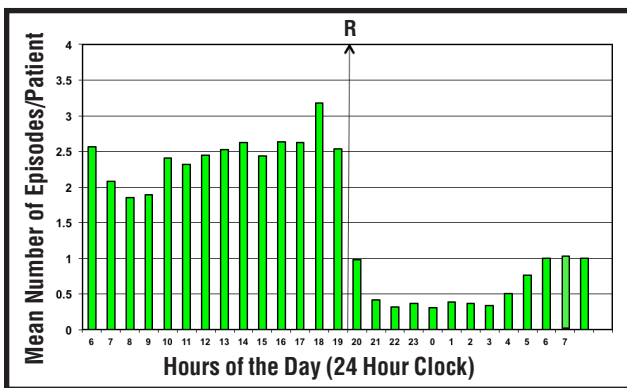
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group (Figure 7A), there was more acid type reflux seen. In contrast, in the 2 on therapy groups (QD and BID)), the number of non- acid type reflux predominates. (Figures 7B and 7C respectively).

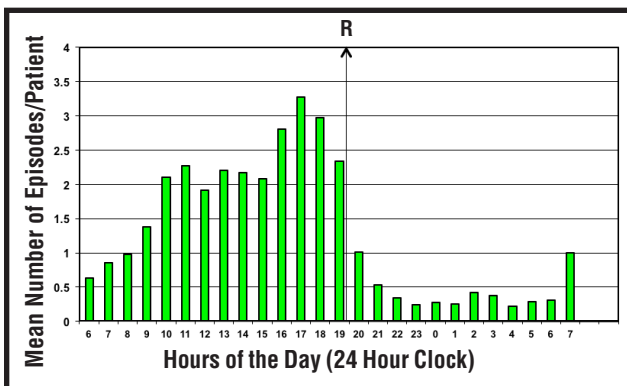
**Figure 4. Comparison of Reflux Episodes Per Hour Between the 3 Groups Aligned Around Beginning of Recumbent Position**



**A: OFF PPI**



**B: QD PPI**



**C: BID PPI**

**DISCUSSION**

Reflux occurs in all individuals and it is affected by position, feeding, and state of wakefulness. Circadian variations shown by Stein in 1990 found no differences in the frequency of esophageal contractions during upright, supine, and meal periods in normal volunteers or patients with GERD.<sup>2</sup> Wang in 1996 found that there were more reflux episodes in the upright than in the supine position<sup>10</sup> in 10 healthy subjects.

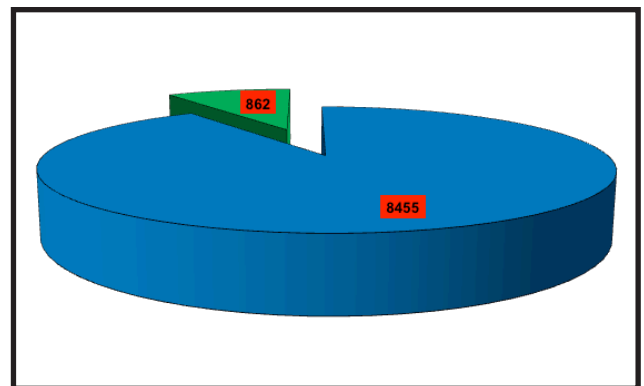
Reflux episodes are believed to be more common at nighttime than in the rest of the day, especially in the early part of the nighttime<sup>11</sup> and are associated with late meals and snacks. Also there is evidence that nighttime GERD has a greater impact on a patient’s life than daytime GERD.<sup>12,13</sup> Moore and Englert found greater rates of acid secretion in the evening with no variation in the serum gastrin levels when compared to the morning levels.<sup>14,15</sup> Sharma et.al.<sup>16</sup> showed that many patients on PPIs still experience GERD symptoms that were frequently associated with non-acid reflux.

An important observation from our data is that circadian patterns of all types of reflux (acid and non-acid) are similar in patients on and off PPI therapy. There is no change in the number of reflux episodes, especially in the upright position, but PPI therapy does change the composition of the refluxate from acid to primarily non-acid in type.

We found that about 90% of reflux episodes occur in the upright position and in the evening related to a meal and the post prandial state. This is not a surprise since transient lower esophageal sphincter relaxations mainly occur in the meal-distended stomach.<sup>17</sup>

There is also a dramatic decrease in episodes with

**Figure 5. Comparison Between Total Reflux Episodes vs Episodes in Recumbent Position**





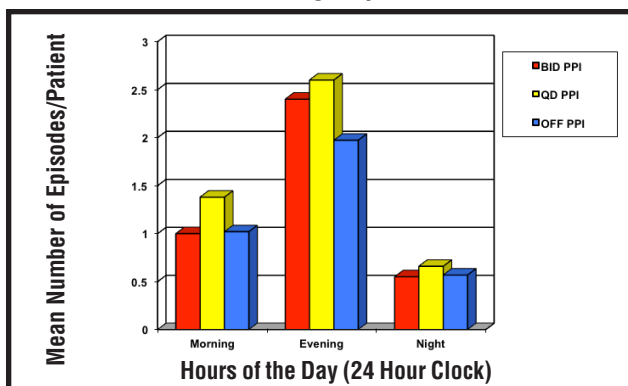
the onset of recumbency, which strengthens the concept of transient lower esophageal sphincter relaxation (TLESR) and suggests that in the recumbent position, the LES contracts to prevent the passage of food and secretions from the stomach to the esophagus.<sup>18</sup>

Our study confirmed the results of prior study done by Tamhankar et.al.<sup>19</sup> Also, it extended the analysis to include the hourly circadian pattern of reflux episodes, both acidic and non-acidic in patients taking different types of PPIs.

Dent et al. in a study of mechanisms of GERD in the recumbent position in 10 healthy volunteers, showed that only 20% of reflux episodes defined by pH level <4 occurred after midnight while the majority occurred within a few hours after the evening meal.<sup>20</sup> Our data confirm and extend that study to patients with suspected GERD symptoms. In addition, the advanced technology provided by combined MII-pH monitoring allows detection of all types of reflux, both acid and non-acid. The latter is particularly important during the post-prandial periods when buffering from the meals produces a milieu where refluxate is largely pH >4.

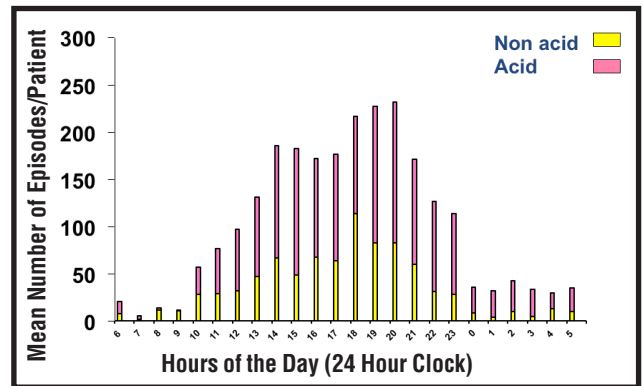
The highest percentage of recumbent episodes occur in the off PPI therapy group probably because during recumbency, which is generally associated with sleep, the normal physiological acid secretion response is not altered by meals, drinks (especially carbonated), stress or changes in positions that is more commonly seen in the upright position or awake. In that way, therapy can be more effective. Also, one should consider that while the patient is sleeping, it will be more difficult to record the symptoms on the tracing unless they are so severe that they awaken the patient.

**Figure 6. Comparison between mean reflux episodes per hour per segment of the day in the 3 treatment groups**

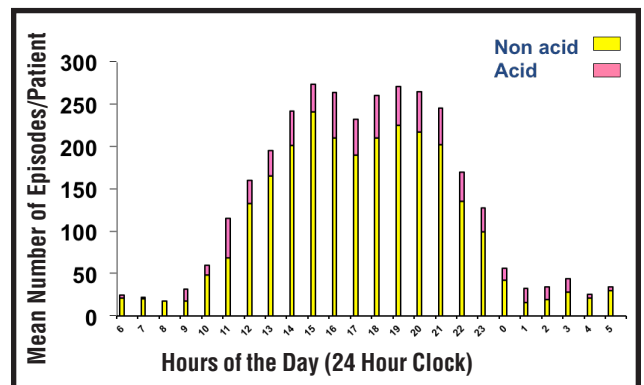


One particular finding from our study was that in the off PPI group, the patients had a trend toward less reflux episodes when compared to the 2 on PPI therapy groups (which was significant between the QD PPI therapy group and the off PPI therapy group in the recumbent position only). This finding was unexpected. Does this mean that PPI therapy increases the number of reflux episodes? One possible explanation for these findings is that the patients taking PPIs had fewer symptoms than

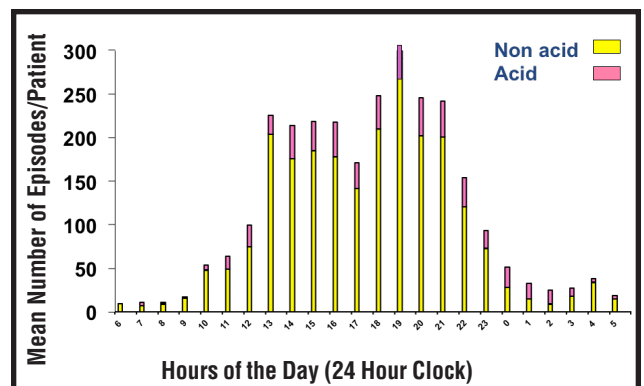
**Figure 7. Total Reflux Episodes Per Hour**



**A: Off PPI (N = 100)**



**B: PPI 1/day (N = 100)**



**C: PPI bid (N = 100)**

patients off PPIs so that they will tend to eat more food and will be more comfortable with having larger meals when compared to the off therapy group.

We did not comment on symptom association with reflux (acidic and nonacidic) in this study as the main goal was to document that PPI therapy does not totally reduce reflux episodes, it only alters the pH of the refluxate. We think that it will be important to consider new therapeutic agents for GERD that could eventually reduce the amount of reflux episodes and not only their composition. ■

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