The Pattern of Esophageal Acid Exposure in Gastroesophageal Reflux Disease Influences the Severity of the Disease

Guilherme M. R. Campos, MD; Jeffrey H. Peters, MD; Tom R. DeMeester, MD; Stefan Öberg, MD; Peter F. Crookes, MD; Rodney J. Mason, MD

Hypothesis: There is an independent association between the different patterns of esophageal acid exposure in gastroesophageal reflux disease and the severity of the disease.

Design: Case-comparison study.

Setting: Department of surgery at a university hospital.

Patients: A group of 401 patients with increased esophageal acid exposure divided into 4 groups according to the pattern of reflux: postprandial (n = 41), upright (n = 74), supine (n = 129), and bipositional (n = 157).

Main Outcome Measures: The prevalence of mucosal injury and the status of the lower esophageal sphincter and esophageal motility were assessed in each group.

Results: The likelihood of having indicators of the severity of gastroesophageal reflux disease increases progressively from postprandial to upright, supine, and bipositional reflux.

Conclusions: The pattern of esophageal acid exposure in gastroesophageal reflux disease is an objective predictor of the severity of disease and could be used for therapeutic decisions.

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Recent studies have shown that the prevalence and severity of gastroesophageal reflux disease (GERD) are increasing.1-4 This is true despite dramatic improvements in the efficacy of treatment options. This “epidemic” increase is at least partially explained by factors such as dietary changes, improved diagnostic techniques, increased awareness, and the widespread availability and use of upper endoscopy. Despite this explanation, there is serious concern that the present therapeutic approach to GERD may not be adequate and the traditional stepwise approach, in which successively more efficacious therapies are used following failure of the previous treatment, deserves reassessment. Ideally, decisions regarding the most appropriate medical or surgical therapy are based on an understanding of the underlying disease severity and the probability of future complications.5-6 This is particularly true in the approximately 50% of patients who present without evidence of esophagitis or other signs of mucosal injury.7-8 Identifying risk factors associated with severe disease allows the clinician to tailor the therapeutic approach prior to the development of complications.

Prolonged esophageal pH monitoring was first reported by Miller10 in 1964, although it was not until 1973 that its clinical applicability and advantages were demonstrated by Johnson and DeMeester.11 It is considered by many to be the criterion standard for the diagnosis of GERD, as it has the highest sensitivity and specificity of all tests currently available. In addition to identifying pathologic esophageal acid exposure, the study quantifies the time that esophageal mucosa is exposed to gastric juice, measures the ability of the esophagus to clear refluxed acid, and correlates esophageal acid exposure with the patient’s symptoms. It is the only way to quantitatively express the overall degree and pattern of esophageal acid exposure.8,12,13 With these facts in mind, we wondered whether the pattern of reflux in GERD could be used as a risk factor to identify patients with severe disease. Thus, we studied the influence of different reflux patterns on the prevalence of mucosal injury, loss of barrier function, and impaired esophageal clearance function.
PATIENTS AND METHODS

The study population consisted of 401 patients evaluated in the Esophageal Laboratory of the University of Southern California, Los Angeles, between August 1991 and June 1998. Pathologic esophageal acid exposure on 24-hour esophageal pH monitoring (composite acid score >14.76) was required for entry into the study. Additional studies included upper gastrointestinal endoscopy with biopsies, video barium esophagogram, and manometry of the lower esophageal sphincter (LES) and esophageal body in all patients. Ambulatory 24-hour esophageal pH monitoring was performed using a glass electrode (Ingold Inc, Urdorf, Switzerland) placed 5 cm above the upper border of the manometrically defined LES.

Patients were divided into 4 groups according to the pattern of reflux (ie, on the basis of the percentage of time the esophageal pH was below 4 in each period and position). The upper limit of normal for esophageal acid exposure in each period and position was defined by the 95th percentile values obtained in asymptomatic volunteers.14,15 These were the groups: postprandial refluxers—patients with abnormal esophageal acid exposure in the 2-hour postprandial period after 2 meals (>8.4%),15 but still with a normal percentage of time the esophageal pH was below 4 in the supine position; upright refluxers—patients with an abnormal percentage of time the esophageal pH was below 4 in the supine position (8.4%), regardless of whether the postprandial exposure was normal or abnormal; supine refluxers—patients with an abnormal percentage of time the esophageal pH was below 4 in the supine position only (>3.4%); and bipositional refluxers—patients with an abnormal percentage of time the esophageal pH was below 4 in both the upright and supine positions. Patients with named motility disorders and those with a history of previous esophageal or gastric operations were excluded from the study.

The distribution of the 401 patients in each group is shown in Table 1. Overall, there were 272 men and 129 women, with a median age of 52 years (range, 15-86 years). There were no differences between the groups regarding age and body mass index. Patients with bipositional reflux had a longer history of reflux symptoms than all other groups; those with upright and supine reflux had a similar duration of symptoms. The prevalence of hiatal hernia (2 cm) in each group is also shown in Table 1.

The characteristics of esophageal acid exposure during 24-hour esophageal pH monitoring in each group are described in Table 2. Patients with bipositional reflux had the most extensive esophageal acid exposure, with all parameters significantly higher than in any other group. The composite acid score increased progressively; patients with postprandial reflux had the lowest score and those with bipositional reflux had the highest score. Although patients with upright reflux had a greater time of esophageal exposure to a pH less than 4 than supine refluxers, their composite acid score was lower, reflecting the presence of longer reflux episodes in patients with supine reflux.

Table 1. Age, Body Mass Index, Duration of Symptoms, and Prevalence of Hiatal Hernia

<table>
<thead>
<tr>
<th>Reflux Pattern</th>
<th>No. (%)</th>
<th>Age, y*</th>
<th>Body Mass Index*</th>
<th>Duration of Symptoms, mo*</th>
<th>Hiatal Hernia, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postprandial</td>
<td>41 (10)</td>
<td>49.5 (43-59)</td>
<td>25.8 (23.1-28.5)</td>
<td>6 (4-12)</td>
<td>13 (32)</td>
</tr>
<tr>
<td>Upright</td>
<td>74 (18)</td>
<td>55.3 (45-66)</td>
<td>26.8 (24.4-30.1)</td>
<td>9 (4-16)</td>
<td>37 (50)</td>
</tr>
<tr>
<td>Supine</td>
<td>129 (32)</td>
<td>49.4 (40-63)</td>
<td>26.5 (24.1-29.3)</td>
<td>10 (4-20)†</td>
<td>84 (65)</td>
</tr>
<tr>
<td>Bipositional</td>
<td>157 (39)</td>
<td>52.7 (43-61)</td>
<td>27.6 (25.6-30.6)</td>
<td>14 (6-21)‡</td>
<td>132 (84)</td>
</tr>
<tr>
<td>Total</td>
<td>401 (100)</td>
<td>52 (43-62)</td>
<td>27.0 (24.4-29.9)</td>
<td>10 (5-20)</td>
<td>266 (66)</td>
</tr>
</tbody>
</table>

*Values are median (interquartile range). Body mass index is calculated by dividing the weight (given in kilograms) by the height (given in meters, squared).
†P = .03 vs patients with postprandial reflux.
‡P = .03 vs all other groups.

Table 2. Characteristics of Esophageal Acid Exposure With Different Patterns of Reflux*

<table>
<thead>
<tr>
<th></th>
<th>Postprandial</th>
<th>Upright</th>
<th>Supine</th>
<th>Bipositional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time pH &lt;4.4%, †</td>
<td>4.8 (4.3-5.5)</td>
<td>8.2 (6.7-10)</td>
<td>6.8 (4.9-9.3)</td>
<td>15.2 (11.2-22)</td>
</tr>
<tr>
<td>Reflux episodes, No.</td>
<td>66 (50-86)</td>
<td>76 (52-110)</td>
<td>67 (39-102)</td>
<td>167 (99-272)‡</td>
</tr>
<tr>
<td>Reflux episodes &gt;5 min, No.</td>
<td>2 (1-3)</td>
<td>4 (3-5)</td>
<td>3 (2-5)</td>
<td>7 (4-11)‡</td>
</tr>
<tr>
<td>Longest reflux episode, min§</td>
<td>9 (6-16)</td>
<td>14 (9-27)</td>
<td>21 (14-30)</td>
<td>24 (14-42)</td>
</tr>
</tbody>
</table>
| Composite acid score§ | 25 (21.3-32.2) | 29 (22-40) | 58 (42.3-85) | }

*Values are median (interquartile range).
†P = .01 between all groups.
§P = .05 vs all other groups.
| A composite acid score greater than 14.76 was considered abnormal.
DEFINITION OF OUTCOME MEASURES

The following outcome measures were recorded: erosive esophagitis, stricture, and esophageal ulcer, Barrett esophagus of any length, and LES and esophageal body motility status.

Endoscopic esophagitis was defined as the presence of linear or confluent erosions in the distal esophagus. Barrett esophagus was defined as the presence of endoscopically visible esophageal columnar lining, regardless of its extent, with histologic confirmation of the presence of intestinal metaplasia. Short-segment Barrett esophagus was defined as when the length of columnar epithelium was less than 3 cm and long-segment Barrett esophagus as when the length was 3 cm or more. Intestinal metaplasia was identified by the presence of well-defined goblet cells within columnar epithelium. Stricture was defined as any non-neoplastic segmental narrowing of the esophagus, excluding esophageal rings and webs.

Lower esophageal sphincter pressure was measured by a stationary pull-through technique at the respiratory inversion point. The resting pressure and overall and abdominal length were calculated from the mean of 5 recordings. A structurally defective sphincter was defined by a resting pressure of less than 6 mm Hg, overall length less than 2 cm, abdominal length less than 1 cm, or any combination of these.

Esophageal body motility was assessed by positioning the catheter’s 5 side holes within the esophageal body, with the most proximal side hole placed 1 cm below the lower border of the upper esophageal sphincter. A total of 10 wet swallows (5 mL of distilled water) with a 20-second interval between each were analyzed. Poor esophageal body motility was defined by the presence of distal esophageal contraction amplitudes below the fifth percentile of normal.

STATISTICS

Values are expressed as median and interquartile range unless otherwise stated. The Fisher exact test was used to compare proportions between groups. A χ² test for linear trend with df = 1 was used to measure progressively increasing risk across all groups. The Kruskal-Wallis test was used to compare the distribution of continuous data between and within the groups. The Mann-Whitney U test was used to compare the distribution of continuous data between individual groups. Statistical significance was determined by α ≤ .05. Stepwise logistic regression was performed to assess the factors significantly associated with mucosal injury. Age, sex, body mass index, duration of symptoms, hiatal hernia, the parameters obtained from the 24-hour esophageal pH monitoring (percentage of time the esophageal pH was < 4 during the total, upright, and supine periods; number of single reflux episodes; number of reflux episodes > 5 minutes; and longest reflux episode), LES competence, and distal esophageal body motility status were examined with this regression procedure. To stay in the model, covariates were required to be significant at α ≤ .05. The significant covariates were then fitted simultaneously in a multivariate model to obtain the predictive effect of each adjusted for the presence of the other significant covariates (adjusted odds ratio [OR]).

The prevalence of mucosal injury with different patterns of reflux is shown in Figure 1. Patients with bipositional reflux had a significantly higher prevalence of mucosal injury than any other group (P ≤ .01). Linear trend analysis showed that there was a progressively increased risk of mucosal injury, including esophagitis, Barrett esophagus, and stricture and/or ulcer across all groups, and that the odds for the presence of mucosal injury are cumulative from postprandial through bipositional reflux (OR, 1.9; 95% confidence interval [CI], 1.6-2.4; P < .001). In addition, patients with bipositional reflux had a greater prevalence of long-segment Barrett esophagus (Figure 2).

The status of the gastroesophageal barrier as measured by the resting characteristics of the LES is shown in Table 4. Sphincter pressure and overall and abdominal lengths were similar in patients with postprandial and upright reflux but were significantly decreased in those with supine and bipositional reflux. The prevalence of a structurally defective LES was significantly higher in patients with supine or bipositional reflux, as shown in Figure 3. Linear trend analysis showed that the prevalence of defective LES increased progressively across all the groups (OR, 1.9; 95% CI, 1.5-2.4; P < .001).

Esophageal clearance function, including median contraction amplitude, number of reflux episodes longer than 5 minutes, and the longest reflux episode, was also significantly worse in patients with supine and bipositional reflux (Table 4). Again, linear trend analysis showed a progressively increasing risk for defective distal esophageal body motility across the groups (OR, 1.7; 95% CI, 1.3-2.2; P < .001).

At the multivariate level, 5 factors were identified as predictors of the presence of mucosal injury. They were an abnormal number of single reflux episodes, the pattern of esophageal acid exposure, the presence of a hiatal hernia, the presence of a defective LES pressure, and

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an abnormal number of reflux episodes longer than 5 minutes (Table 5). Note that the pattern of esophageal acid exposure continues to be a significant independent risk factor for the presence of mucosal injury after adjusting for other factors using the multivariate analysis.

It is accepted that the severity of GERD as measured by presence and type of mucosal injury is related to the presence of a structurally defective LES, the degree and extent of esophageal acid exposure, and the esophageal clearance function.7,12,16,17 The relationship between the pattern of the acid exposure in GERD and the severity of the disease, however, is not well demonstrated. In patients with GERD, 24-hour esophageal pH monitoring readily identifies 4 different patterns of esophageal acid exposure. These include patients who have reflux predominantly in the period following meals (postprandial reflux), in the upright or in the supine period only, and throughout the 24-hour recording cycle (i.e., in both the upright and supine periods [bipositional reflux]). The results of this study confirm a correlation between the pattern of reflux and the severity of reflux disease.

Logistic regression analysis showed that the risk of esophageal mucosal injury increased progressively from postprandial to bipositional reflux. Patients with bipositional reflux were significantly more likely to have mucosal injury than patients with postprandial, upright, or supine reflux; 78% had endoscopic evidence of mucosal injury. Equally important was the finding that more than one third of patients with isolated postprandial reflux also had mucosal injury. Given that such patients have relatively limited esophageal acid exposure, this fact suggests that other factors, such as the composition of the refluxate, also play a role.17

Barrett esophagus has emerged as an important clinical feature associated with gastroesophageal reflux disease, and its diagnosis is increasing.18,19 It is now recognized to occur in short (<3 cm) segments of endoscopically recognizable intestinal metaplasia as well as the traditional long-segment form (≥3 cm). The reasons underlying the development of short segments in some patients and long segments in others remain unclear. We found that long-segment Barrett esophagus is more likely to occur in patients with bipositional reflux, while this not so for patients with short-segment Barrett esophagus.
induced transient relaxation of the sphincter. In contrast, bipositional reflux was associated with a structurally normal sphincter or to neurologically defective LES and impaired esophageal clearance during sleep, when upright. However, patients with supine reflux have defective esophageal clearance during sleep, caused by esophageal inactivity, and this can result in mucosal injury.

The results of this study suggest that the pattern of esophageal acid exposure in GERD influences the severity of the disease and can be used as an additional prognostic factor for therapeutic decisions.

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We thank our validating statistician, Silvia Tan, MS, Department of Biometry, University of Southern California, Los Angeles.

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**REFERENCES**


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**Table 4. Esophageal Clearance Function With Different Patterns of Reflux**

<table>
<thead>
<tr>
<th>Reflux Pattern</th>
<th>Distal esophageal contractions, mm Hg</th>
<th>Reflux episodes &gt;5 min, No.</th>
<th>Longest reflux episode, min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postprandial</td>
<td>66 (50-119)</td>
<td>2 (1-3)†</td>
<td>9 (6-16)§</td>
</tr>
<tr>
<td>Upright</td>
<td>69 (51-103)</td>
<td>4 (3-5)</td>
<td>14 (9-27)</td>
</tr>
<tr>
<td>Supine</td>
<td>61 (40-88)</td>
<td>3 (2-5)</td>
<td>21 (14-30)</td>
</tr>
<tr>
<td>Bipositional</td>
<td>47 (32-74)†</td>
<td>7 (4-11)†</td>
<td>24 (14-42)</td>
</tr>
</tbody>
</table>

*Values are median (interquartile range).
†P ≤.05 vs all other groups.
‡P ≤.01 vs all other groups.
§P ≤.05 between all groups.

**Table 5. Stepwise Logistic Regression Results for Predictors of Mucosal Injury**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio (95% CI)†</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal No. of single reflux episodes</td>
<td>4.0 (2.1-7.8)</td>
<td>.001</td>
</tr>
<tr>
<td>Pattern of esophageal acid exposure</td>
<td>1.8 (1.5-2.5)</td>
<td>.001</td>
</tr>
<tr>
<td>Hiatal hernia</td>
<td>2.3 (1.4-3.9)</td>
<td>.001</td>
</tr>
<tr>
<td>Abnormal LES pressure</td>
<td>2.1 (1.3-3.5)</td>
<td>.002</td>
</tr>
<tr>
<td>Abnormal No. of reflux episodes &gt;5 min</td>
<td>2.1 (1.3-3.5)</td>
<td>.004</td>
</tr>
</tbody>
</table>

*CI indicates confidence interval; LES, lower esophageal sphincter.†The odds ratio for each positive predictor is adjusted for the presence of all other predictors in the model.
Carl M. Pellegrini, MD, Seattle, Wash: In the September 1976 issue of the Annals of Surgery, Dr DeMeester and his collaborators1 published a landmark paper on the pathophysiology of reflux. The authors identified in that paper 3 patterns among patients who have GERD, those who refluxed only in the upright position, the so-called upright refluxers, those who refluxed primarily in the supine position (supine refluxers), and those who refluxed in both positions (then called the combined refluxers). The authors also examined the new causal injury associated with this different pattern and the outcome of surgery in these individuals. Dr Campos and his collaborators have revisited Dr DeMeester’s original observations, studying a larger cohort of patients. As one contrasts this study with the original one, 2 important aspects emerge. First, the authors have confirmed the existence and the relative frequency of these well-defined patterns among patients who have reflux disease. They have also confirmed the fact that mucosal injury is much more prevalent among patients with combined or so-called bipositional reflux. Second, there are some new concepts introduced in this paper. One of them is the existence of postprandial reflux, and the other one is a concept of a progression of disease rather than having different forms of the disease.

My questions will revolve around these new observations. The first one has to do with postprandial reflux, and I will address that in just a second, and then I will make a couple of comments on the upright part. We have been led to believe, originally by Dr DeMeester and then by several other individuals who used 24-hour pH monitoring, that the postprandial time is part of the upright component of reflux. Since the authors have now described postprandial reflux as a different entity, is it then time to change the 24-hour pH monitoring to a 3-component part—postprandial, upright, and supine—rather than leaving the postprandial merged with the upright reflux, which makes the identification of these patients a bit more difficult?

Eighteen percent of your patients were upright refluxers. In the past, upright reflux has been seen as a mild form of disease, one that was usually not associated with esophagitis and, in fact, one that was associated with gas bloat after operations. We have recently compared our experience on 34 patients with upright reflux with 276 patients that had either combined or bipositional reflux, and we have been struck by 2 facts. Number 1: of the 34 patients with upright reflux, 3 had Barrett esophagus and 3 presented with strictures, so that patients with upright reflux have indeed a perhaps more severe form than we had expected. Number 2: operative therapy in these patients achieved essentially the same symptomatic relief as achieved in the 276-patient cohort that had bipositional or combined reflux.

So upright reflux is no longer a contraindication for operation in our group. We did observe, however, a higher incidence of gas bloat among patients who had upright reflux. Since you have now also found Barrett esophagus in upright refluxers, could you tell us how many of the patients that you reported today with upright reflux had an operation, and, if so, would you tell us what the outcome of that operation was?

An additional curiosity is that in the original paper there was a finding of aspiration associated with the supine type of reflux, something that we have also continued to observe in our current experience, and I wonder if you could mention what was the incidence of either laryngeal or pulmonary complications among the different patterns.

Finally, you have advanced a concept of a progression of this disease. Most of us have been used to thinking of upright and supine reflux as 2 manifestations of an incompetent cardia. Assuming that there is a progression then from postprandial all the way through bipositional reflux, and since there appears to be an increasing prevalence of mucosal injury through this disease, do you then advocate performing an operation at an earlier stage to prevent this problem? In other words, would it be appropriate to operate on patients who have only the postprandial type of reflux?

Gastroesophageal reflux is one of the most common disorders affecting men and women of the Western world today. Understanding the pathophysiology, the pathogenesis, of the natural history is very important to plan appropriate therapy. With many effective forms of therapy available today and some very new ones coming up on the horizon, the information presented here today by Dr Campos is vital to the practicing surgeon.

Lawrence Way, MD, San Francisco, Calif: In recent years, patients with heartburn often receive acid-reducing agents, such as H2 blockers or proton pump inhibitors, before their first endoscopy, and they have nearly always had such treatment for prolonged periods before being referred to a surgeon for consideration of antireflux surgery. As a result, the mucosal damage that might otherwise result from acid reflux is mitigated and may be entirely eliminated by this point. Other than for detecting Barrett disease, endoscopy has been of progressively declining value in our experience for diagnosing and gauging the severity of reflux disease. Consequently, I wonder why in your patients there still seems to be a close correlation between the endoscopic and physiologic abnormalities?

Dr Peters: Let me first point out that the emphasis of this paper was on identifying risk factors for severe disease, although we also think there are significant pathophysiologic insights to the patterns of reflux. As Dr Campos pointed out, we believe firmly that the idea that one should escalate reflux therapy progressively needs to fall by the wayside. Rather, we should treat these patients more like cardiologists treat heart disease patients and assess their risk.
Let me get to Dr Way’s question first, that is, does treatment affect the mucosal injury patterns? The answer is yes. We are not seeing the natural history of the disease. That is one of the reasons why we think it is important to identify high-risk patterns. As the treatment variables get more and more complex, the underlying reflux pattern can help us to elucidate the patient’s overall risk and hopefully to make therapeutic decisions based on that. Yes, we believe that the treatment affects the prevalence of mucosal injury, although the data would suggest that perhaps not as much as one might intuitively suspect. We still see a significant cohort with mucosal injury, 80% almost in the bipositional reflux, as you saw.

To address Dr Pellegrini’s questions, we believe that postprandial reflux is an emerging entity. One of the things the laparoscope has prompted is the referral of a lot more patients with early disease. The therapeutic decisions in those patients are more difficult. One needs as much objective evidence as possible to help make the decision between antireflux surgery and continued medical therapy. The pH probe can help to pick out those patients. Many patients with isolated postprandial reflux are significantly symptomatic. They should be separated from the upright group.

Is there an outcome difference when we operate on patients with upright reflux only? I don’t think so, although as you pointed out, perhaps there is a slight difference in the side effects, such as gas bloat. Last year, at another one of the regional meetings, one of our fellows, Martin Fein, looked at the question of the outcome of laparoscopic fundoplication in patients with upright reflux. We found no difference in patients with upright reflux vs those with other patterns.

About half of the patients in this group were operated on. The best we can tell, the outcome was not different between the 2 groups with respect to the relief of reflux symptoms.

Yes, there is a significant incidence of mucosal injury in patients with earlier disease. There was one patient with Barrett esophagus in the postprandial group, and in the upright group there was a 35% incidence of mucosal injury. That points out that the pattern of reflux is only one of the risk factors. Other factors are important, such as the status of the sphincter, the contact time, and the composition of the refluxate. These factors likely explain the fact that in patients with postprandial or upright reflux there still is an incidence of mucosal injury.

Again, our focus here was on severe disease as an indication for surgery rather than on relatively early disease and its pathophysiology. Finally, Dr Pellegrini, I do think we should be operating on patients at an earlier stage in order to prevent these complications. The ultimate treatment for Barrett esophagus is prevention, just like the ultimate treatment for lung cancer is prevention. We would like to get into the phase where we are now selecting patients based on their risk and potentially preventing strictures, ulcers, and Barrett esophagus rather than treating them once they have occurred. This gets back to what I originally said about approaching the disease with a risk analysis.