

Correlation of 24-Hr Esophageal pH Patterns with Clinical Features and Endoscopy in Gastroesophageal Reflux Disease

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We performed 24-hr ambulatory esophageal pH monitoring in north Indian patients with gastroesophageal reflux disease (GERD) and correlated it with symptom severity and endoscopic abnormalities. Thirty-six consecutive patients with symptomatic GERD and 16 healthy volunteers underwent objective grading of clinical symptoms and endoscopic findings. Total, supine, and upright reflux periods as well as frequency and duration of reflux episodes were determined from the 24-hr pH-metry record using standard software. This was abnormal in 32 patients, who could be categorized into upright refluxers (31.2%), supine refluxers (34.4%), and combined refluxers (34.4%). Supine reflux and upright reflux were distinct entities that did not correlate with each other ($r = 0.22$, $P = NS$). In upright refluxers, symptoms ($P < 0.02$) and endoscopic abnormalities ($P < 0.005$) were milder than in combined refluxers. Total duration of acid exposure correlated significantly with severity of symptoms ($P < 0.001$) and endoscopic esophagitis ($P < 0.005$). Patients with GERD had three distinct patterns of abnormal gastroesophageal reflux, with upright refluxers having milder disease and supine and combined refluxers having more severe disease. This may reflect differences in underlying mechanisms of reflux.

KEY WORDS: gastroesophageal reflux; reflux patterns; pH monitoring.

Prolonged ambulatory pH-metry allows esophageal pH monitoring during routine daily activities and also permits quantification of severity of reflux. While minimal gastroesophageal reflux (GER) may be seen even in healthy individuals, patients with gastroesophageal reflux disease (GERD) experience significantly longer and more frequent reflux episodes (1). While some workers (1, 2) have noted distinct patterns of reflux in symptomatic patients, others (3, 4) have failed to find such patterns. The

role of daytime reflux in the development of complications of GERD has been emphasized by some (3), while others (1, 5) have suggested prolonged nocturnal reflux is the important factor. We therefore undertook a prospective study to identify patterns of abnormal reflux among Indian patients with GERD using 24-hr pH monitoring and tried to correlate these patterns with severity of symptoms and endoscopic abnormalities.

MATERIALS AND METHODS

Patients. Thirty-six consecutive patients (27 men, 9 women; age range 19–70 years, mean 41.9) with symptoms of gastroesophageal reflux disease for at least six months were studied. Symptoms were assessed to be absent, mild, moderate, or severe. They were scored as follows—(i) heartburn: no heartburn, 0; occasional epi-

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sodes, 1; reason for medical visit, 2; interference with daily activities, 3; (ii) regurgitation: no regurgitation, 0; occasional episodes, 1; predictable on position or straining, 2; episodes of pulmonary aspiration, 3; (iii) dysphagia: no dysphagia, 0; occasional episodes, 1, liquids required to clear, 2; episodes of bolus impaction, 3; and (iv) chest pain: no chest pain, 0; occasional episodes, 1; reason for medical visit, 2; interference with daily activities, 3. Heartburn (30 patients) and/or regurgitation (20 patients) were present in all cases. None of them had any other abnormality on upper gastrointestinal endoscopy or on abdominal sonography, and none had undergone abdominal surgery. Coronary artery disease was excluded in patients with atypical chest pain ($N = 7$) by negative electrocardiogram, treadmill test, or coronary angiography. All patients underwent upper gastrointestinal endoscopy, and esophagitis was classified from grades 1 to 4 (6): grade 1, localized hyperemia, with or without exudates; grade 2, confluent exudate and erosions not involving full circumference; grade 3, erosions involving full esophageal circumference; and grade 4, presence of complications such as peptic stenosis, Barrett's esophagus, etc. H_2 -receptor blocker (six patients) and prokinetic drugs (four patients) were discontinued at least 48-hr before the study.

Healthy Volunteers. Sixteen age- and sex-matched healthy volunteers (11 men, 5 women; age range 17–62 years, mean 34.8) without any symptoms of abdominal disease and without any systemic illness or previous abdominal operations were chosen as controls. They had normal upper gastrointestinal endoscopy, esophageal mucosal histology, and ultrasound examination. All patients and subjects underwent ambulatory 24-hr pH monitoring.

24-Hr pH Monitoring. This was done using the Aspen portable pH-metry unit consisting of a glass pH electrode (diameter 4.0 mm) and a portable solid state data logger. Using a sampling frequency of one sample every 10 sec the memory of the data logger box permitted pH monitoring for a period slightly exceeding 22 hr in all individuals. After calibration in buffer solutions at pH 7 and 4, the electrode was introduced through the nose and placed 5 cm above the proximal margin of the gastroesophageal junction located earlier by esophageal manometry and endoscopy in all healthy volunteers and in 24 patients, and by endoscopy alone in 12 patients. Where the gastroesophageal junction was located by endoscopy, 5 cm were added to correct for the extra length of the nasopharyngeal route (7). Volunteers and patients were upright in the daytime and went to bed 2 hr after dinner. During the study, the subject noted events (meals, upright and supine position, pain, or special event) on a diary card and in the data logger. Volunteers and patients ate four meals (lunch, evening tea, dinner, and breakfast) during the monitoring period and were requested not to smoke or take coffee, alcohol, or acidic drinks. They were asked to continue their usual activities during waking hours. After the study, end calibration was done *in vitro*. The data recorded were transferred to a computer and analyzed by standard software. A reflux episode was considered to begin when pH fell below 4 and end when pH reverted to 4 or above. Five parameters were calculated separately for upright, supine, and combined periods: percentage of

time with esophageal pH < 4, number of reflux episodes, mean duration of reflux episodes, number of reflux episodes lasting longer than 5 min, and duration of longest reflux episode.

Abnormal gastroesophageal reflux was present when the percentage of total time with pH less than 4 (acid exposure time) exceeded the 95th percentile of the range obtained in healthy volunteers. Patients were further classified as upright, supine, or combined refluxers when acid exposure time exceeded the 95th percentile of the range obtained in healthy volunteers in corresponding positions.

Statistics. Various parameters of the 24-hr pH record in healthy volunteers and patients as well as severity of esophagitis and symptoms in patients with various patterns of reflux were compared using the Wilcoxon rank-sum test. Pearson's correlation coefficient was used to find the relationship between severity of symptoms or esophagitis and esophageal acid exposure time.

RESULTS

Reflux Patterns. Of the 36 patients studied, four patients had a normal 24-hr pH record (Figure 1). Thirty-two patients with abnormal 24-hr pH records could be categorized as upright refluxers ($N = 10$), supine refluxers ($N = 11$), and combined refluxers ($N = 11$) (Figure 1).

Twenty-four-hour pH monitoring of the distal esophagus showed that among healthy volunteers, gastroesophageal reflux was not uncommon and was not associated with any symptom. Total acid exposure time ranged from 0.0% to 3.0% (median 1.8%). Physiologic acid reflux episodes occurred more often in the upright position (Figure 2). Total acid exposure time was longer ($P < 0.01$) and reflux episodes were more frequent ($P < 0.01$) in the upright position (Figures 2 and 3), although duration of reflux episodes was no different between upright and supine positions (Figure 4).

The number of upright reflux episodes was higher in upright refluxers than in healthy volunteers ($P < 0.000001$), while there was no difference in number of supine reflux episodes. Similarly, in supine refluxers, the number of supine reflux episodes was more frequent ($P < 0.02$) than in healthy volunteers. In combined refluxers, the number of reflux episodes both in upright ($P < 0.000005$) and supine ($P < 0.00005$) positions were more frequent than in healthy volunteers (Figure 3).

In upright refluxers, duration of upright and supine reflux episodes did not differ significantly from controls (Figure 4). However, supine refluxers ($P < 0.00001$) and combined refluxers ($P < 0.0001$) had markedly prolonged supine reflux episodes com-

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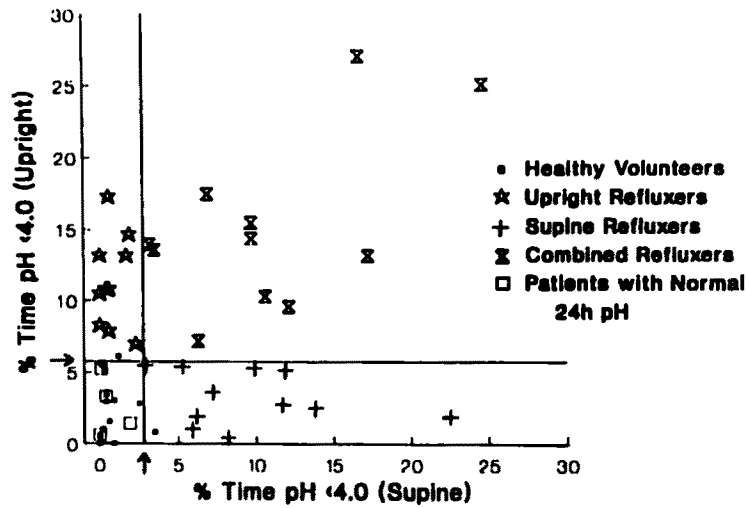


Fig 1. Scattergram showing distribution of upright and supine esophageal acid exposure time in healthy volunteers and patients; 95th percentile values (arrows) for esophageal acid exposure in supine and upright periods in healthy volunteers are depicted.

pared to controls (Figure 4). Mean duration of supine reflux episodes in supine refluxers was also significantly longer than in upright refluxers ($P < 0.0001$) and combined refluxers ($P < 0.01$).

Acid exposure time during both upright and supine periods of 24-hr pH recording correlated well with acid exposure time during the total 24-hr period ($r = 0.81$, $P < 0.000001$; $r = 0.72$, $P < 0.000001$, respectively). Acid exposure time in up-

right and supine periods did not correlate with each other ($r = 0.22$, $P = NS$), implying that upright and supine reflux are distinct and independent entities.

Symptoms and Reflux Patterns. The frequency and severity of heartburn, regurgitation, dysphagia, and chest pain for each reflux pattern is shown in Figure 5A. Severe heartburn and regurgitation were seen only in supine and combined refluxers. Chest pain occurred with all patterns of reflux, but was

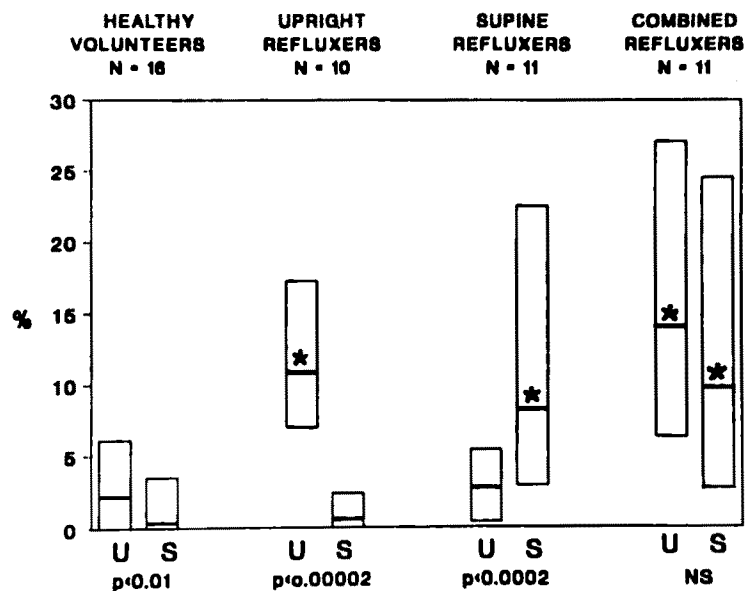


Fig 2. Comparison of acid exposure time in upright, supine, and combined refluxers with healthy volunteers. U, upright period; S, supine period; * $P < 0.000001$.

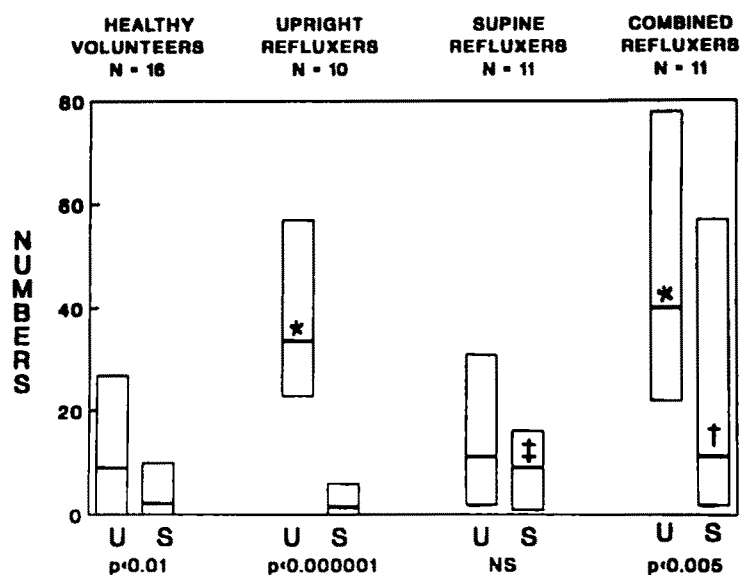


Fig 3. Comparison of number of reflux episodes in upright, supine, and combined refluxers with healthy volunteers. U, upright period; S, supine period; * $P < 0.000005$, † $P < 0.00005$, ‡ $P < 0.02$.

twice as common in combined refluxers as in either upright or supine refluxers. Dysphagia was also seen with all patterns of reflux. Combined refluxers had more severe symptoms than upright refluxers ($P < 0.02$), while no difference was observed between upright and supine refluxers or between supine and combined refluxers (Table 1). Patients with a normal 24-hr pH record ($N = 4$) had mild symp-

toms. None of them had dysphagia or chest pain. Total duration of acid exposure correlated with severity of symptoms ($r = 0.53$; $P < 0.001$).

Endoscopic Findings and Esophageal pH. Esophagitis was detected at esophagoscopy in 25 patients (grade I in 11, grade II in 9, and grade III in 5). Of 11 patients with grade I endoscopic esophagitis, two had a normal 24-hr pH record. None had grade IV

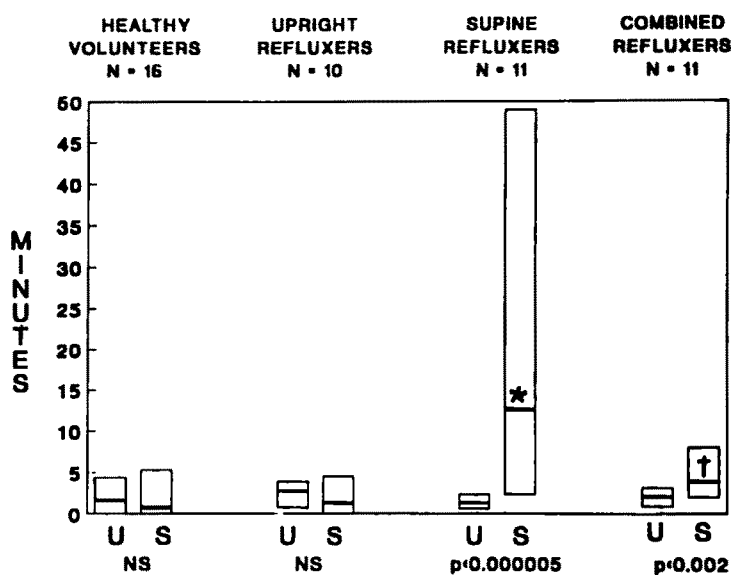


Fig 4. Comparison of mean duration of reflux episodes in upright, supine, and combined refluxers with healthy volunteers. U, upright period; S, supine period; * $P < 0.00001$, † $P < 0.0001$.

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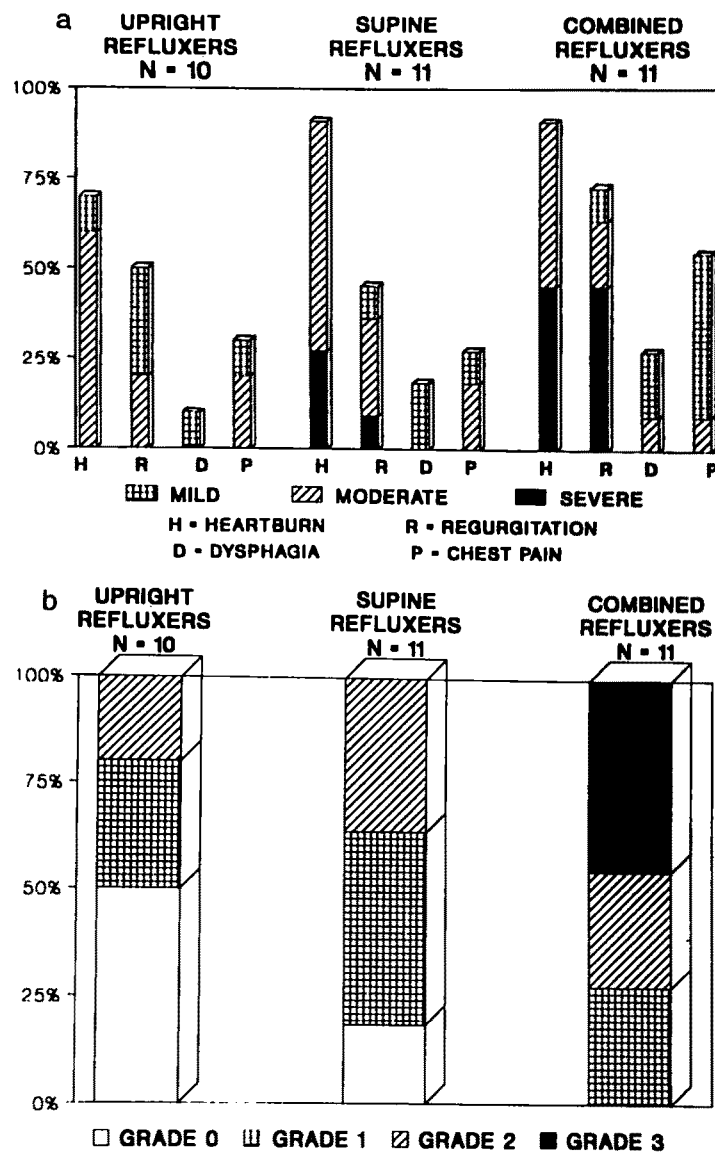


Fig 5. (a) Frequency and severity of symptoms, and (b) endoscopic grading of esophagitis in patients with upright, supine, and combined patterns of gastroesophageal reflux.

esophagitis according to Savary and Miller (6) (Figure 5B). Esophagitis was more severe in combined

TABLE 1. COMPARISON OF SEVERITY OF SYMPTOMS AND ENDOSCOPIC ESOPHAGITIS IN DIFFERENT CATEGORIES OF REFLUXERS

Pattern of reflux	Symptoms score median (range)	Endoscopic grade median (range)
Upright	2.5 (1-5)*a	0.5 (0-2)c
Supine	3.0 (1-6)	1.0 (0-2)b
Combined	5.0 (2-9)a	2.0 (0-3)b,c

*a, $P < 0.02$; b, $P < 0.05$; c, $P < 0.005$ (Wilcoxon rank-sum test).

refluxers ($P < 0.005$) and in supine refluxers ($P < 0.05$) than in upright refluxers (Table 1). Total duration of acid exposure correlated with severity of esophagitis ($r = 0.47$, $P < 0.005$).

DISCUSSION

Ambulatory esophageal pH monitoring showed that even healthy volunteers experienced gastroesophageal reflux. Most of this physiologic reflux occurred in the upright position and in the form of

TABLE 2. GASTROESOPHAGEAL REFLUX IN HEALTHY INDIAN, AMERICAN, AND ITALIAN VOLUNTEERS [MEAN \pm (SD)]

Study	pH < 4 (%)			Number of reflux episodes	Episode > 5 min	Longest episode (min)
	Total	Upright	Supine			
Present (N = 16)	1.5 (1.1)	2.3 (2.0)	0.7 (1.0)	13.5 (10.8)	0.7 (0.8)	5.0 (3.0)
American (9) (N = 15)	1.5 (1.4)	2.3 (1.9)	0.3 (0.5)	20.6 (14.8)	0.6 (1.2)	3.9 (2.7)
Italian (10) (N = 15)	1.7 (1.4)	2.7 (3.2)	0.8 (1.1)	25.5 (17.4)	0.6 (1.0)	4.6 (3.1)

brief episodes. These observations are similar to those previously reported (Table 2) (5, 8).

We could clearly classify our patients with symptomatic reflux into three groups based on the posture in which abnormal reflux occurred: (1) upright or (2) supine refluxers who had reflux mainly in upright or supine position, respectively, and (3) combined refluxers who had reflux in both positions. Esophageal acid exposure in the upright and supine periods each correlated significantly with total 24-hr acid exposure. However, no correlation was found between upright and supine reflux periods, suggesting that both were independent and distinct entities. Upright refluxers had numerous brief episodes of reflux, and their mean duration did not differ significantly from healthy volunteers in either position (Figures 3 and 4). Supine refluxers experienced prolonged reflux episodes in the supine position, the median duration of these episodes (12.5 min) being significantly longer than in all other categories of patients (Figure 4). The longest reflux episode in this group was as much as 49.0 min (Figure 4). Combined refluxers had numerous episodes of prolonged supine reflux in addition to numerous brief upright reflux episodes and experienced the longest periods of distal esophageal acid exposure. Our observations also suggest that short-term ambulatory pH monitoring schedules, such as 3-hr daytime postprandial monitoring suggested by some workers (3, 9, 10), may fail to identify supine refluxers, who form almost one third of our patients with GERD, and 37% of patients in the series of DeMeester et al (1).

We also observed that upright refluxers had the mildest symptoms, while combined refluxers had the most severe symptoms (Figure 5A). While none of the upright refluxers had severe symptoms, supine refluxers often had severe heartburn and regurgitation. Combined refluxers exhibited severe symptoms even more frequently. Similarly, upright refluxers had the mildest grades of endoscopic

esophagitis, while combined refluxers had the most severe grades of endoscopic esophagitis, with grade 3 esophagitis being noted only in combined refluxers (Figure 5B). Total duration of esophageal acid exposure correlated significantly with symptom score ($r = 0.53$, $P < 0.001$) and endoscopic grading of esophagitis ($r = 0.47$, $P < 0.005$).

Similar patterns of reflux in patients with GERD have also been reported by other workers (1, 2). DeMeester et al (1) noted that combined reflux was the most frequent pattern (54%) in their 100 patients, followed by supine reflux (37%), and upright reflux (9%). In contrast, we found the three patterns equally frequently in our population. However, our observation that the greatest severity of symptoms and endoscopic esophagitis was seen in combined refluxers while mildest symptoms and endoscopic abnormalities were noted in upright refluxers was in accordance with the findings of DeMeester et al (1). Vitale et al (2) also characterized their patients as erect (26%), supine (23%), or combined refluxers (51%), but they did not correlate these patterns with severity of symptoms and failed to find any correlation with severity of endoscopic abnormalities. Other workers (3, 4) failed to discern distinct patterns in their patients and have noted good correlation between erect and supine reflux periods. Early studies on patterns of reflux were criticized on the grounds of lack of precise quantification of abnormal supine reflux (1, 2, 11), restricted mobility of patients during monitoring (1, 2) or poor food intake by the patient during monitoring (3). The latter two factors would possibly minimize daytime reflux. However, our observation of distinct posture-related patterns in patients who were fully ambulatory and who did not restrict their intake supports occurrence of such distinct patterns.

It is thus important to explain the differences in the findings of those studies (1, 2), which have found distinct patterns of reflux as have we, and others (3, 4), which have failed to observe them. It

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is difficult to consider geographical or ethnic factors. The most likely factor seems to be study bias. The high proportion of upright refluxers in our study (31.2%) contrasts with figures of 9% (1) and 26% (2) in other studies. Similarly we had only 34.4% combined refluxers as compared to 54% (1) and 51% (2) reported elsewhere. Overall, Indian patients with GERD seem to be younger, have milder disease, and develop fewer complications than Western patients. Similar bias might have crept into other studies, which have shown findings similar to ours. On the basis of existing knowledge of the pathophysiology of GERD, it may be speculated that in upright refluxers, the predominant mechanism of reflux is an increased frequency of transient lower esophageal sphincter relaxations (TLESRs) with relatively preserved acid clearance from the distal esophagus (12). On the other hand, the major abnormality in supine refluxers is a marked impairment in acid clearance from the distal esophagus due to a combination of factors such as elimination of gravity (13), sleep (14), and diminished salivary secretion (15). Combined refluxers probably exhibit both abnormalities and, correspondingly, have severe reflux disease. Whatever the underlying mechanism of reflux, injury to the distal esophageal mucosa is a function of total duration of acid exposure. Confirmation of these speculations needs correlation with esophageal manometric findings in each category of refluxers and simultaneous ambulatory pH-metry and manometry for correlating reflux episodes with TLESRs.

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