ALIMENTARY TRACT

Acid, Nonacid, and Gas Reflux in Patients With Gastroesophageal Reflux Disease During Ambulatory 24-Hour pH-Impedance Recordings

DANIEL SIFRIM,* RICHARD HOLLOWAY,† JIRI SILNY,§ ZHANG XIN,* JAN TACK,* ANTOON LERUT,* and JOZEF JANSSENS*

*Centre for Gastroenterological Research, University of Leuven, Leuven, Belgium; †Department of Gastroenterology, Hepatology, and General Medicine, Royal Adelaide Hospital, Adelaide, South Australia; and §Helmoltz-Institute for Biomedical Engineering, Aachen, Germany

See editorial on page 1862.

Background & Aims: **Gastroesophageal reflux can be acid, nonacid, pure liquid, or a mixture of gas and liquid. We investigated the prevalence of acid and nonacid reflux and the air-liquid composition of the refluxate in ambulant healthy subjects and patients with reflux disease (GERD).** ***Methods:*** **Twenty-four–hour ambulatory recordings were performed in 30 patients with symptomatic GERD and erosive esophagitis and in 28 controls. Esophageal pH and impedance were used to identify acid reflux (pH drop below 4.0), minor acid reflux (pH drop above 4.0), nonacid reflux (pH drop less than 1 unit + liquid reflux in impedance), and gas reflux.** ***Results:*** **The total rate of gastroesophageal reflux episodes was similar in patients and controls. Patients with GERD had a higher proportion (45% vs. 33%) and rate of acid reflux than controls (21.5 [9–35]/24 h vs. 13 [6.5–21]/24 h; $P < 0.05$). One third of reflux events was nonacid in both groups. Mixed reflux of gas and liquid was the most frequent pattern with gas preceding liquid in 50%–80% of cases. Pure liquid reflux was more often acid in patients with GERD than controls (45% vs. 32%; $P < 0.05$).** ***Conclusions:*** **Reflux of gastric contents was similarly frequent in patients with GERD and controls. Although there was no difference in the overall number of reflux episodes, more acidic reflux occurred in symptomatic patients with GERD, suggesting differences in gastric acid secretion or distribution.**

It is generally accepted that patients with gastroesophageal reflux disease (GERD) have more acid reflux episodes than healthy subjects.[1–5] Up to now, concepts about the frequency of gastroesophageal reflux and efficiency of the antireflux barrier have been based on inferences derived from measurement of esophageal pH and manometric markers of reflux such as the common cavity.[6–11] Gastric fundic contents may have variable acidity and composition depending on the gastric secretory status, the time after the meal, and/or the distribution of gastric contents. Thus the refluxate may be acid, nonacid, liquid, or gas.[12]

Until recently, information about the composition of the refluxate has been limited to acid and bile because specific markers of nonacid liquid and gas reflux have not been available. In combination with pH monitoring, recording of esophageal intraluminal electrical impedance can distinguish between acid and nonacid liquid and gas gastroesophageal reflux.[12–17] Using this approach in normal adult subjects in resting sitting position, we have shown recently that transient lower esophageal sphincter (LES) relaxations were the main mechanism for both acid and nonacid gastroesophageal reflux.[12] A subsequent study in patients with GERD showed no significant differences from normal subjects in rate of transient LES relaxations and total number of reflux events, but patients with reflux disease had more acid reflux, less nonacid reflux, and a higher proportion of pure liquid reflux compared with healthy subjects.[17]

The gastric distribution of gas, liquids, and solids is highly influenced by the body position, which might in turn modify the air-liquid patterns of reflux. In resting sitting subjects, at least half of acid reflux episodes are associated with reflux of gas.[12–17] However, a significant proportion of reflux episodes was either pure liquid or mixed reflux of liquid and gas with liquid preceding the gas, suggesting that acid reflux can be a primary event rather than a consequence of belching. Our previous

Abbreviations used in this paper: GERD, gastroesophageal reflux disease; LES, lower esophageal sphincter.

© 2001 by the American Gastroenterological Association

0016-5085/01/$35.00
doi:10.1053/gast.2001.24841

studies, however, were performed postprandially in resting sitting subjects. This is not representative of the normal pattern of posture during the day, which involves periods of recumbency and upright physical activity as well as sitting. Posture has been shown to have a significant effect on patterns of reflux[18–24] as well as on lower esophageal sphincter function.[7,24–26] Physical activity also increases the degree of reflux.[27–31] It is possible, therefore, that patterns of acid and nonacid, or gas and liquid, reflux under ambulatory conditions might differ from those under stationary conditions.

The aims of this study were to investigate the prevalence of acid and nonacid gastroesophageal reflux and the air-liquid composition of the refluxate under ambulatory conditions in normal healthy subjects and patients with GERD.

Materials and Methods

Subjects

Ambulatory 24-hour combined esophageal pH and impedance recordings were performed in 28 healthy controls (16 men, 12 women; median age, 31 years; range, 21–68 years) and in 30 patients with GERD (19 men, 11 women; median age, 45 years; range, 19–73 years). All the patients had erosive esophagitis (Savary–Miller grade I, 14 patients; grade II, 8 patients; grade III, 3 patients); 5 patients had uncomplicated Barrett's esophagus. Twelve patients had a hiatus hernia proven by endoscopy. None of the patients had undergone previous gastrointestinal surgery or was taking medication known to influence esophageal motor function. Acid suppression medication was stopped at least 1 week before the study. In 4 patients, therapy was interrupted 72 hours before the study. The study was approved by the University Hospital Ethics Committee and written informed consent was obtained from all subjects.

Intraluminal Electrical Impedance and pH

Intraluminal electrical impedance was recorded with a 2.3-mm diameter polyvinyl assembly containing a series of cylindrical electrodes, each 4 mm in axial length and spaced at 2-cm intervals. Each pair of electrodes formed a measuring segment, 2 cm in length, corresponding to 1 recording channel. Esophageal pH was measured with antimony pH electrodes incorporated into the assembly. The combined assembly included 1 pH sensor to be located 5 cm proximal to the LES and 4 impedance segments spanning the distal and midesophageal body (Figure 1).

The pH-impedance assembly was connected to a portable device that contained the pH amplifiers and impedance-voltage transducers that delivered a measuring current of 3 μamps at a frequency of 1000–1600 Hz (prototype developed by Prof. Jiri Silny at the Helmholtz-Institute for Biomedical Engineering, Unit of Technology, Aachen, Germany). The pH and impedance signals were recorded by a separate digital datalogger that sampled the analog signals at 200 Hz per channel (GSM, Filderstad-Bonlanden, Germany). Before the start and at the end of the recording, the pH electrodes were calibrated using pH 1.0 and pH 7.0 buffer solutions.

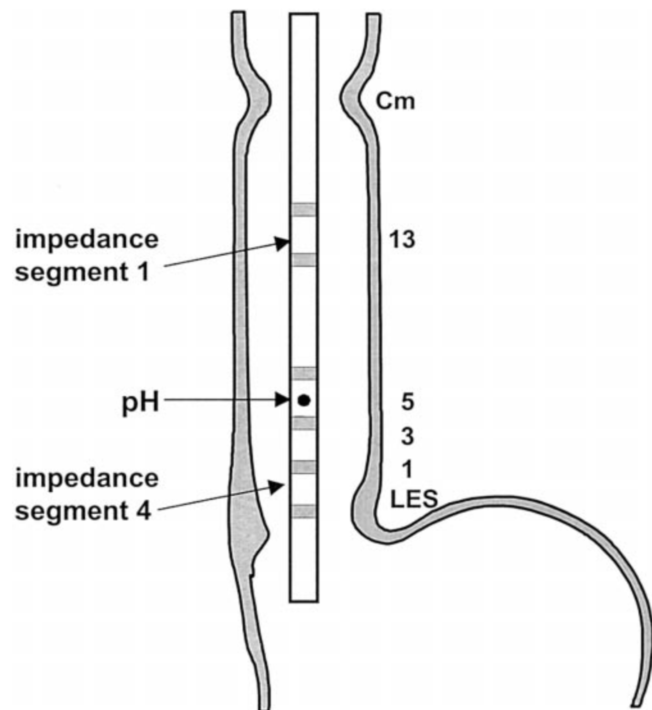

Figure 1. Schematic representation of the recording assembly. The catheter included 1 pH sensor located 5 cm proximal to the LES and 4 impedance segments spanning the distal and midesophageal body.

Study Protocol

The subjects were studied after an overnight fast of at least 10 hours. Before the ambulatory study, all subjects underwent a stationary esophageal manometry to determine the location of the LES. After the stationary manometry, the combined pH-impedance assembly was passed through the nose under topical anesthesia and positioned with the proximal pH electrode at 5 cm above the LES. In this position, the midpoints of the impedance recording segments were located at 1, 3, 5, and 13 cm proximal to the LES.

During the 24-hour study, the subjects were in the upright position during the day and were allowed free movement and 1 recumbent period. All subjects had 3 standardized liquid meals, each consisting of a 400-mL nutrient drink (600 kcal, 13% protein, 39% carbohydrate, 48% fat; Nutridrink; Nutricia, Netherlands). The liquid meal was chosen to promote homogeneous mixing of gastric contents. The subjects were instructed to fill out a diary indicating the times of the meals and supine position.

Data Analysis

The 24-hour pH-impedance recording was uploaded into a personal computer and displayed on a single screen for

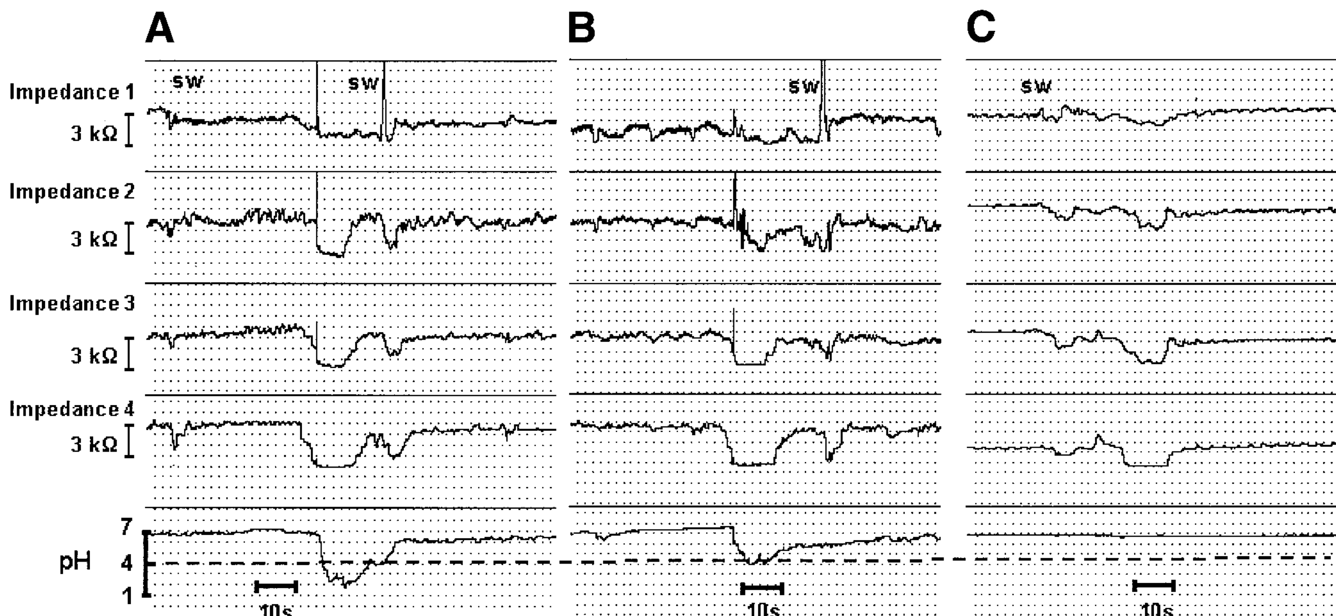

Figure 2. Tracings of concurrent esophageal impedance and esophageal pH. (*A*) Traditional acid reflux, mixed gas-liquid. Esophageal pH falls from above to below pH 4. The impedance tracing shows an initial abrupt rise indicative of gas reflux followed by a very fast retrogradely propagated drop consistent with liquid reflux. (*B*) Minor acid reflux, mixed gas-liquid. Esophageal pH falls more than 1 pH unit but remains above 4. The impedance tracing shows an initial abrupt rise indicative of gas reflux followed by a very fast retrogradely propagated drop consistent with liquid reflux. (*C*) Nonacid reflux, pure liquid. The impedance tracing shows a retrogradely propagated drop consistent with liquid reflux. There is no significant esophageal pH change. SW, swallow.

computer-assisted manual analysis, using a dedicated software program (Review; A Andrioli, K.U. Leuven, Belgium). The pH recording was analyzed for reflux episodes. All abrupt falls in pH (within a time frame of 8 seconds) of at least 1 pH unit were identified and counted. Falls in pH were classified as "traditional" acid reflux if pH fell below 4 for at least 4 seconds or, if pH was already below 4, as a decrease of at least 1 pH unit sustained for more than 4 seconds (Figure 2*A*). Minor acid reflux was defined as a pH drop of at least 1 pH unit sustained for more than 4 seconds with the basal pH remaining above 4 (Figure 2*B*). Reflux was judged to be nonacid when there was impedance evidence of reflux but the pH drop was less than 1 pH unit (Figure 2*C*).

The impedance recording was analyzed on the basis of previous studies in the human esophagus[14–16] and our validation studies.[12] Liquid reflux was defined as a sequential orally progressing drop in impedance to less than 40% of the baseline values starting distally at segment 4 (1–3 cm above LES) and propagating retrogradely to at least the next 2 more proximal measuring segments (Figure 2*C*). Gas reflux was defined as a rapid (3 kohms/sec) increase in impedance, occurring simultaneously in at least 2 esophageal measuring segments, in the absence of swallowing (Figure 2*A* and *B*). For each reflux episode as determined by pH and/or impedance, the associated gas-liquid pattern was classified as: (1) mixed reflux of liquid and gas or (2) pure liquid reflux. Pure gas reflux (belches) were not included in the reflux analysis. The proximal extent of each reflux event was evaluated from the impedance tracings. The percent of reflux episodes that reached the impedance segment 1, located 13 cm proximal to LES, was calculated in each subject.

To analyze a possible relationship between severity of reflux disease and different patterns of reflux, patients were divided based on the endoscopic finding into 2 groups: patients with mild reflux disease who exhibited erosive esophagitis (Savary–Miller grade I, 14 patients), and patients with severe reflux disease who had evidence of esophagitis grade II, grade III, and/or Barrett's esophagus (16 patients). Patients were also divided based on their predominant symptom into 2 groups: patients with typical esophageal symptoms, heartburn, and/or regurgitation (22 patients), and patients with predominant extraesophageal symptoms, laryngitis, nocturnal cough, and/or hoarseness (8 patients).

Statistical Analysis

Data for each variable were determined for each patient and medians (interquartile range) calculated for each group. The rates of reflux episodes and the frequency of different impedance/pH patterns of reflux in controls and patients with reflux disease were analyzed and compared using unpaired Mann–Whitney *U* test. The Fisher exact test was used to compare differences between proportions, and the Kruskal–Wallis test followed by Dunn's multiple comparisons test were used to assess the influence of severity of reflux disease and hiatal hernia on reflux patterns. A P value of < 0.05 was considered to be significant.

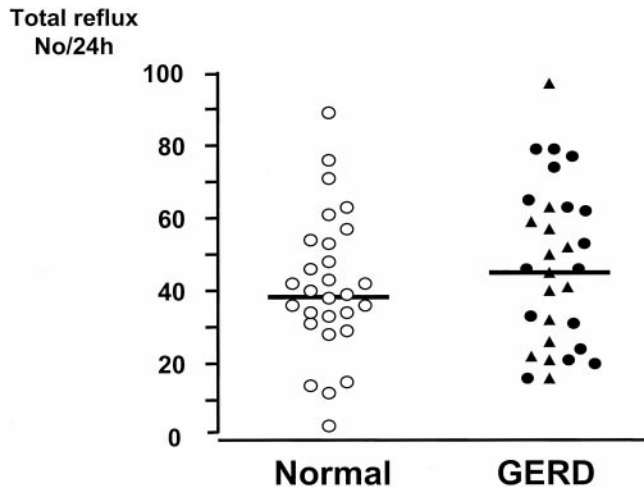

Figure 3. Frequency distribution of total number of gastroesophageal reflux episodes in healthy subjects (○) and patients with mild (▲) and severe (●) reflux disease (GERD).

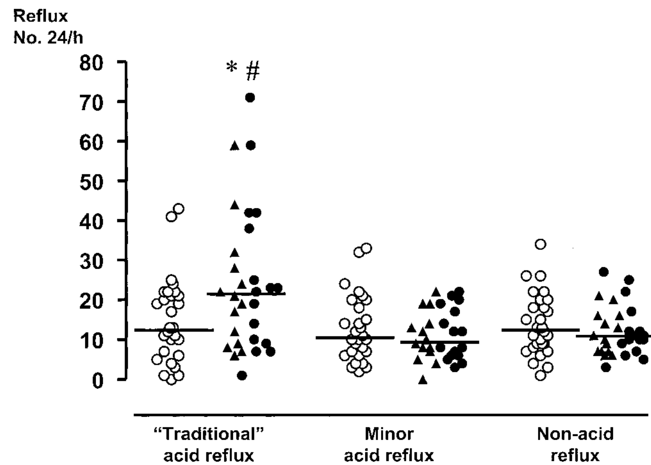

Figure 4. Frequency distribution of the different types of gastroesophageal reflux episodes (traditional acid, minor acid, and nonacid) in healthy subjects (○) and patients with mild (▲) and severe (●) GERD. *$P < 0.05$ vs. controls; #$P < 0.05$ vs. minor and nonacid reflux.

Results

The impedance-pH probe was well tolerated and comparably to other pH and manometry assemblies used for ambulatory pH measurements. The total recording time was 23.2 (22.7–23.6) hours in controls and 23.5 (22.8–24) hours in patients with reflux disease. Meal periods (3 periods of approximately 15 minutes) were excluded from the analysis. The impedance recordings showed a stable baseline in each measuring segment. The main difficulties in interpretation of impedance tracings were accumulation of air in the proximal esophagus and low baseline impedance values in the more distal esophagus in patients with Barrett's esophagus.

When all gastroesophageal reflux events are considered (traditional acid, minor acid, and nonacid reflux), the total rate of reflux episodes was not significantly different in patients with reflux disease (46 [25–64]/24 hours) compared with controls (39.5 [32–53]/24 hours) (Figure 3). However, patients with reflux disease had a significantly higher rate of traditional acid reflux (21.5 [9–35]/24 hours vs. 13 [6.5–21]/24 hours; $P < 0.05$) (Figure 4). Furthermore, the proportion of traditional acid reflux from the total number of reflux episodes was higher in patients with reflux disease compared with controls (45 [35%–56%] vs. 33 [24%–45%]; $P < 0.05$). The duration of traditional acid reflux was significantly longer in patients with reflux disease compared with controls (44.6 [23–77] vs. 23.9 [14–43] seconds; $P < 0.05$). There were no differences among the rates and proportions of traditional acid, minor acid, and nonacid reflux episodes in healthy controls. In patients with reflux disease, however, the rate and proportion of traditional acid reflux were significantly higher than those of minor acid and nonacid reflux (Figure 4 and Table 1).

Patterns of Gas and Liquid Reflux

Impedance changes associated with traditional acid reflux. In healthy subjects, the majority (82% [68%–92%]) of traditional acid reflux episodes were associated with impedance evidence of mixed reflux of liquid and gas. Likewise, in patients with reflux disease, mixed reflux was predominant, but it was less frequent (68% [50%–84%]; $P < 0.05$) than in controls and the proportion of pure liquid reflux (31.5% [16%–49%]) was higher than in controls (17 [6.5%–26%]; $P < 0.05$) (Figure 5).

During mixed traditional acid reflux, gas reflux frequently preceded reflux of liquid in both groups, but this pattern was significantly more frequent in patients

Table 1. Proportion of Different Types of Gastroesophageal Reflux and the Air-Liquid Pattern of Total Reflux During the 24-Hour Recording

	Controls (N = 28)	Patients (N = 30)
% Time pH < 4	1.3 ± 0.3	3.4 ± 0.5[a]
Total reflux		
% Traditional acid	33 (24–45)	45 (35–56)%[a,b]
% Minor acid	29 (23–38)	25 (16–33)%
% Nonacid	33 (25–47)	28 (18–39)
Total reflux		
% Liquid reflux	48 (33–51)	38 (27–52)
% Mixed reflux	52 (49–66)	62 (48–73)
% Gas-liquid	70 (50–85)	76 (64–89)
% Liquid-gas	30 (15–50)	24 (10–35)

[a]$P < 0.05$ vs. controls.
[b]$P < 0.05$ vs. minor acid and nonacid reflux.

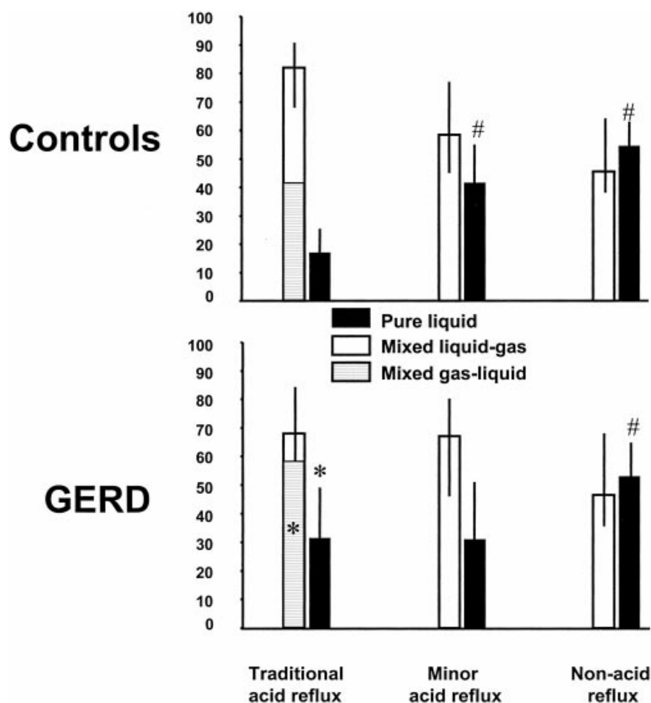

Figure 5. Proportion of different impedance patterns of pure liquid and mixed refluxate during traditional acid, minor acid, and nonacid reflux in healthy controls and patients with GERD. *$P < 0.05$ vs. controls; $^{\#}P < 0.05$ vs. traditional acid reflux.

(84.5% [69%–97%]) with reflux disease than in controls (50% [33%–89%]; $P < 0.05$) (Figure 5).

Impedance changes associated with minor acid reflux. Minor acid reflux was predominantly mixed reflux of liquid and gas in controls (58.5% [45%–77%] of events) and in patients (67% [46%–80%] of events). The air-liquid pattern of minor acid reflux did not differ significantly between controls and patients. However, in controls, but not in patients, minor acid reflux was more frequently pure liquid than was traditional acid reflux (Figure 5).

Impedance changes associated with nonacid reflux. Nonacid reflux contained pure liquid more frequently than did traditional acid reflux (Figure 5). For mixed reflux, there were no differences in air-liquid composition between controls and patients with reflux disease (Figure 5).

Impact of Age, Severity of Reflux Disease, and Hiatus Hernia on Patterns of Reflux

There was no influence of age on the frequencies of acid and nonacid reflux or the air-liquid patterns of refluxate. Neither severity of esophagitis nor presence of hiatus hernia influenced the relative distribution of acid and nonacid reflux. During traditional acid reflux, patients with more severe esophagitis and hiatus hernia had the highest percent of liquid refluxate, and during mixed reflux they had the highest prevalence of reflux of gas preceding reflux of liquid. However, there were no statistically significant differences between patients with mild and severe reflux disease or between those with and without hiatus hernia (Table 2).

Proximal Extent of Reflux

The proportion of traditional acid reflux episodes in which the refluxate reached the most proximal impedance segment did not differ between controls and patients but was significantly greater than that for nonacid reflux episodes both in controls (48% [16%–62%] vs. 21% [2%–41%]; $P < 0.05$) and in patients with reflux

Table 2. Impact of Age, Severity of Reflux Disease, and Hiatus Hernia on Patterns of Reflux

	Patients with reflux disease					
	Age		Severity		Hiatus hernia	
	<35 years (N = 7)	>55 years (N = 8)	Mild GERD (N = 14)	Severe GERD (N = 16)	No (N = 18)	Yes (N = 12)
All reflux (events/24 h)	52 (33–72)	46 (28–75)	47.5 (28–58)	46 (22–69)	51 (32–63)	36 (21–65)
% Traditional acid	56 (48–69)	46 (37–58)	45 (35–56)	44 (35–56)	45 (35–56)	44 (38–56)
% Minor acid	18 (10–27)	27 (22–35)	26 (17–31)	25 (15–37)	25 (19–33)	23 (11–35)
% Nonacid	20 (19–48)	23 (16–40)	26 (19–34)	27 (16–42)	28 (19–37)	24 (16–40)
All reflux						
% Liquid reflux	35 (24–54)	38 (28–52)	35 (22–52)	44 (30–52)	35 (24–54)	48 (33–51)
% Mixed reflux	65 (50–80)	62 (49–76)	65 (47–77)	56 (48–69)	64 (46–76)	51 (48–66)
% Gas-liquid	78 (72–90)	74 (68–92)	70 (64–86)	85 (66–90)	76 (64–90)	77 (64–89)
% Liquid-gas	22 (13–33)	26 (10–37)	30 (13–35)	15 (9.5–34)	24 (9.5–35)	22 (11–36)
Traditional acid reflux						
% Liquid reflux	41 (17–52)	40 (22–51)	24 (14–47)	36 (21–51)	23 (14–46)	43 (24–54)
% Mixed reflux	59 (53–87)	60 (51–82)	75.5 (53–85)	64 (48–78)	77 (53–86)	57 (46–75)
% Gas-liquid	91 (79–100)	85 (69–100)	77 (62–88)	89 (76–100)	77 (62–91)	91 (82–100)
% Liquid-gas	9 (2.5–32)	15 (3–35)	23 (11–38)	10.5 (0–24)	23 (8.5–38)	8.5 (0–17)

Table 3. Effect of Body Position on Patterns of Reflux

	Controls		Patients	
	Upright	Supine	Upright	Supine
All reflux	2.6 (1.9–3.3)/h	0.4 (0.2–0.8)/h	2.6 (1.4–3.8)/h	0.5 (0.1–0.8)/h
% Traditional acid	34 (25–45)	0 (0–28)	46 (35–58)[a]	38 (7–79)[a]
% Minor acid	27.5 (20–38)	29 (0–40)	27 (17–34)	8 (0–20)[a]
% Nonacid	32.5 (19–46)	58 (36–79)	24 (16–35)	43 (10–75)
Traditional acid reflux	0.8 (04–1.4)/h	0 (0–0.2)	1.2 (0.5–2.3)	0.17 (0–0.5)[a]
% Liquid reflux	36 (9–50)	62 (16–91)	26 (13–47)	67 (50–100)
% Mixed reflux	64 (62–93)	38 (8–83)	74 (52–86)	33 (0–50)
% Gas-liquid	68 (50–84)	100 (100–100)	85 (73–100)[a]	100 (75–100)
% Liquid-gas	32 (16–50)	0 (0–0)	15 (0–26)	0 (0–25)
Minor acid reflux	0.6 (0.3–1.1)/h	0.1 (0–0.2)/h	0.6 (0.3–1)/h	0 (0–0.1)/h
% Liquid reflux	38.5 (14–53)	60 (0–100)	31 (16–50)	100 (0–100)
% Mixed reflux	61.5 (48–87)	40 (0–100)	68 (48–83)	0 (0–100)
% Gas-liquid	56 (32–84)	100 (100–25)	75 (50–93)	100 (50–100)
% Liquid-gas	44 (15–67)	0 (0–75)	25 (13–50)	0 (0–50)
Nonacid reflux	0.6 (0.4–1.1)/h	0.26 (0–0.4)/h	0.6 (0.4–0.8)/h	0.17 (0–0.3)/h
% Liquid reflux	44 (25–55)	100 (75–100)	41 (27–55)	100 (63–100)
% Mixed reflux	56 (44–74)	0 (0–30)	59 (44–72)	0 (0–36)
% Gas-liquid	85 (63–100)	100 (100–100)	82 (41–100)	100 (0–50)
% Liquid-gas	15 (0–40)	0 (0–25)	15 (0–52)	0 (0–50)

[a] $P < 0.05$ vs. control.

disease (48% [29%–72%] vs. 31% [20%–47%]; $P < 0.05$). Minor acid and nonacid reflux events had higher proximal extent in patients than in controls (49% [28%–64%] vs. 29.5% [0%–52%]; $P < 0.05$ and 31% [20%–47%] vs. 21% [2%–41%], respectively). Nonacid reflux had the lowest proximal extent in both groups. The severity of esophagitis and the presence of hiatal hernia did not affect the proximal extent of reflux.

Recumbent Position and Patterns of Reflux

The rate of total reflux events in recumbent position was similar in controls (0.4 [0.2–0.8]/hour) and patients with reflux disease (0.5 [0.1–0.8]/hour). However, patients with reflux disease had a significantly higher rate of recumbent traditional acid reflux than did controls (0.17 [0–0.5]/hour vs. 0 [0–0.2]/hour; $P < 0.05$). In controls, almost all recumbent reflux episodes were nonacid or minor acid; in contrast in patients with reflux disease (38% [7%–79%]) of recumbent reflux episodes were traditional acid ($P < 0.05$ vs. control).

The air-liquid pattern of recumbent reflux differed significantly from that observed during upright reflux (Table 3). Whereas in upright reflux more than 60% of episodes were mixed reflux of liquid and gas, the majority (80%) of recumbent reflux events were pure liquid. There were no significant differences in air-liquid patterns of supine reflux between patients with reflux disease and controls.

Liquid Reflux: Acid vs. Nonacid

In patients with reflux disease, pure liquid reflux was more frequently traditional acid than in controls. When all pure liquid reflux events were pooled together, 249 of 548 (45%) episodes were traditional acid reflux in the patients group compared with 164 of 512 (32%) observed in the healthy controls ($P < 0.05$). However, there were no differences in the proportions between minor acid reflux (23% vs. 29%) and nonacid reflux (32% vs. 39%).

During the first postprandial hour after the first meal (at noon), impedance evidence of liquid gastroesophageal reflux (with and without air) was found with a similar frequency in patients with reflux disease and controls (5 [3.5–7.5]/hour vs. 5.5 [3–7]/hour). The proportions of traditional acid (28% vs. 29%), minor acid (32% vs. 31%), and nonacid reflux (40% vs. 40%) did not differ between patients and controls.

Predominant Symptoms and Patterns of Reflux

Patients with predominant extraesophageal symptoms (laryngitis, nocturnal cough, or hoarseness) had similar patterns of acid, nonacid, and gas and liquid reflux than those with predominant heartburn and regurgitation (Table 4).

Discussion

This is the first study using ambulatory 24-hour recording of concurrent intraesophageal pH and impedance in healthy subjects and patients with reflux disease. We aimed to analyze the prevalence of acid and nonacid reflux and the air-liquid patterns of the refluxate in

Table 4. Patterns of Reflux in Patients With Predominant Atypical GERD Symptoms

	Typical symptoms (N = 22)	Atypical symptoms (N = 8)
All reflux (events/24 h)	55.5 (38–76)	44 (21–58)
% Traditional acid	51.6 (47–58)	42 (33–53)
% Minor acid	25 (20–28)	26 (12–38)
% Nonacid	19 (16–25)	29 (19–42)
Traditional acid reflux		
Proximal extent % events to LES-13	45 (26–69)	63.5 (38–73)
% Liquid reflux	24 (18–41)	37 (15–52)
% Mixed reflux	76 (58–82)	63 (48–84)
% Gas-liquid	89 (77–55)	82 (63–100)
% Liquid-gas	11 (5–23)	18 (0–37)

patients with reflux disease taking into account the effects of daily physical activity. The results are in part consistent with our previously published reports using stationary postprandial manometry–pH-impedance[12,17] and confirms that, compared with controls, patients with reflux disease have a similar total rate of reflux episodes but a significantly higher rate and proportion of more acidic reflux events, a higher proportion of pure liquid acid reflux, and a liquid reflux that is more likely to be acid. Nonacid reflux represents one third of all gastroesophageal reflux events in healthy subjects and patients with reflux disease. In contrast to the previous stationary studies, however, reflux of liquid followed reflux of gas in half of the events in normals and most of the events in patients with reflux disease. These findings support the notion that some acid reflux may be the consequence of belching.

It is generally accepted that normal subjects with a "competent" antireflux barrier may have a few physiologic acid reflux episodes,[1,32] whereas patients with reflux disease have more reflux events[1–5] suggesting an "incompetent" antireflux barrier.[33,34] The total rate of acid reflux episodes, however, has not been widely adopted as a measure of reflux disease because of its poor reproducibility,[35] poor correlation with severity of esophagitis,[5] and difficulty in defining a reflux episode.[36] Nevertheless, this variable is an important indicator of the competence of the antireflux barrier and is therefore relevant when evaluating the effect of therapies directed at improving the antireflux barrier function. Theoretically, a failure of the antireflux barrier would allow for reflux of any available fundic content regardless of its pH, and surgical or pharmacologic intervention on the gastroesophageal junction area should prevent any type of reflux.

In this study, combining pH and impedance recordings permitted the identification of reflux events of high, moderate, and no acidity. Contrary to the popular view, patients with reflux disease did not have an increased total number of reflux episodes, confirming our previous finding in patients studied in resting sitting position during the postprandial period.[17] The lack of increased number of total reflux events in these patients argues against a severe and fundamental "incompetence" of their antireflux barrier.

It is possible that the size and composition of the meal might have influenced the absolute number of reflux events. Both controls and patients with reflux disease had fewer acid reflux events compared with ambulatory pH studies using mixed liquid-solid meals. The liquid meal used might be a less intense refluxogenic stimulus in both groups. However, even with a lower refluxogenic effect, patients with reflux disease had significantly more traditional acid reflux than controls. The liquid meal was chosen to optimize the mixing of gastric contents because of observations on patterns of reflux in our previous stationary study.[17] It is possible that using mixed meals would increase the total number of reflux episodes in both groups or influence the relative frequency of acid reflux events. Undergoing studies using nonstandardized mixed meals will clarify the role of gastric mixing and relative distribution of food and acid on the patterns of gastroesophageal reflux.

In both ambulatory and stationary studies, the refluxate in patients with reflux disease was significantly more likely to be acidic, which is consistent with the accepted idea of an increased number of acid reflux episodes defined as a fall in pH below 4. This apparent selective defect in acid reflux raises the possibility of other factors other than simple gastroesophageal incompetence contributing to the increased rate of acid reflux episodes.

The duration of traditional acid reflux episodes was significantly longer in patients with reflux disease compared with controls. This parameter is, at best, an indirect reflection of patterns of reflux because it is determined primarily by esophageal clearance. However, the duration of reflux episodes could also be influenced by the volume of the refluxate, which in turn could be related to the degree of LES opening during the reflux event. Further studies measuring the volume of refluxate in patients with reflux disease are needed to confirm this hypothesis.

The air-liquid pattern of reflux in ambulatory conditions differed from that observed in our previous stationary studies[12,17] in which we found a significant number of acid reflux events that were either not associated with impedance evidence of gas or were mixed reflux with liquid preceding gas. These findings suggested that acid

reflux could be a primary event and were not just the consequence of belching. In contrast, under ambulatory conditions, most acid reflux events, both in controls and patients with reflux disease, were mixed of gas and liquid and, during mixed reflux, gas preceded liquid in half of events in normals and most of episodes in patients with reflux disease. These results are in partial agreement with earlier ambulatory manometric-pH studies.[9,10] In healthy subjects and patients with reflux disease, reflux of gas during belching and reflux of acid share a common underlying mechanism, transient LES relaxation.[37,38] The higher proportion of mixed reflux and the increased number of events with gas preceding liquid in the more physiologic ambulatory condition, supports the concept that acid reflux may, at least in part, be the consequence or variant of belching.[9,10] The differences between our stationary and ambulatory studies can probably be attributed to a different distribution of gastric air, and/or patterns of straining during daily activity. Posture has been shown to have a significant effect on patterns of reflux[18–24] as well as on lower esophageal sphincter function.[7,24–26] Physical activity also increases the degree of reflux.[27–31]

A major reason for the increased rate of acid reflux episodes in patients with reflux disease seems to be that, when reflux occurs, the refluxate is more acidic. The factors that make the refluxate more acid in patients with reflux disease are not clear and were not investigated in this study. However, there are a number of possibilities. First, there may be a selective dysfunction of the antireflux barrier when confronted to more acidic gastric contents. Transient LES relaxations are more often associated with acid reflux in patients with reflux disease than in healthy subjects[17,34,39–42] and they are more frequently associated with acid reflux than with nonacid reflux.[17] The acidity of gastric contents can influence the frequency and duration of transient LES relaxations.[43] In our previous stationary study, we observed that the duration of transient LES relaxations was significantly longer when associated with traditional acid reflux compared with nonacid liquid reflux.[17]

Second, there may be an increased gastric acid volume. It has been reported that, as a group, patients with reflux disease do not have a significant increase in basal, meal-stimulated, or maximal gastric acid secretion.[44] More recent studies, however, suggested that some patients with reflux disease may have an increased basal acid secretion,[45] and a multivariate logistic regression analysis of the main variables associated with reflux esophagitis showed that acid secretion level is an independent pathophysiological factor.[46] Studies on gastric emptying and proximal gastric function have suggested that patients with reflux disease may have an enhanced or prolonged postprandial fundic relaxation and a delayed emptying of the proximal stomach.[47,48]

Third, differences may exist in the degree of mixing of fundic contents leading to different distributions of acid in the stomach. It is not clear whether or not the acid is homogeneously mixed with the meal and follows the same pattern of emptying.[49] Studies using ambulatory pH and esophageal scintigraphy[50] and gastric magnetic resonance imaging[51] suggest that gastric mixing can be incomplete, and different layers of viscosity within the stomach might therefore influence the distribution of the gastric contents.[52]

Intraluminal impedance is able to detect small volumes of liquid reflux of neutral pH that are not detected by the pH sensor. Combining impedance with pH monitoring permits the detection of most reflux episodes: very acid (pH below 4), moderately acid (pH 4–6), and nonacid (pH between 6 and 7). A pH drop below 4 is usually taken as evidence of acid gastroesophageal reflux because pepsin is inactive above pH 4[53] and patients with symptomatic reflux generally report heartburn at an esophageal pH below 4.[54] Based on this definition of acid reflux, all other reflux events could be categorized as nonacid reflux. However, reflux episodes associated with falls in esophageal pH that do not fall below 4 may be associated with symptoms such as heartburn and regurgitation.[11,34,55] Therefore, to understand the clinical and physiologic significance of nonacid reflux, we deemed only those events that were associated with a pH drop of <1 pH unit to be nonacid reflux. This more rigid definition differs from that of others, which have deemed all reflux that does not reduce esophageal pH below pH 4 as nonacid.[56]

Recent studies using pH-impedance recordings in infants have shown a high prevalence of nonacid reflux in babies with severe respiratory symptoms.[57] Our results suggest that nonacid reflux does not seem to be critical for the pathogenesis of reflux disease in adults. Using our more stringent definition of nonacid reflux, only one third of all reflux events were nonacid in both groups and there were no significant differences in rate or proportion of nonacid reflux between patients and controls. Furthermore, in patients with reflux disease, traditional acid reflux was significantly more frequent than nonacid reflux. Using the less rigorous definition (all reflux events with pH above 4), nonacid reflux comprises more than half of total reflux episodes, but nevertheless, there are still no significant differences between patients and controls.

In our previous stationary study, we used a mixed solid-liquid meal and found a higher proportion of nonacid reflux in healthy subjects than in reflux disease. In the present study, 40% of reflux episodes during the first hour after the meal were nonacid in both groups. The use of a liquid meal and the ambulant condition might have led to better mixing of gastric content resulting in similar percent of nonacid reflux in patients and normals. Whereas recumbent reflux in normal subjects was mostly minor acid and nonacid, in patients with reflux disease, recumbent nonacid reflux was less frequent than in controls and traditional acid reflux made up 40% of supine events. These findings suggest either a different nocturnal pattern of acid secretion or mixing in the proximal stomach in reflux disease.

The pathophysiological relevance of nonacid reflux in reflux disease is still unknown, but our data would suggest that it does not play a role in the development of esophageal mucosal damage because patients with reflux disease have similar rate and air-liquid patterns of nonacid reflux than normals. The clinical relevance, however, might be more important, particularly as a cause of persistent symptoms in patients while on acid suppressant therapy[56] or in patients with endoscopy-negative reflux disease.

It has been shown that the proximal extent of acid reflux is higher in patients with reflux disease than in healthy subjects.[58] This is also true for nonacid reflux. The proximal extent of nonacid reflux, however, was significantly lower than that of acid reflux, suggesting a smaller volume of liquid refluxate or a stronger tonic response of the esophageal body to reduce the proximal extension of reflux.[59]

Recent evidence has supported the long-held belief that hiatus hernia impairs the antireflux barrier.[60–62] Patients with hiatus hernia have more acid reflux events[63,64] and frequent additional reflux events during esophageal acid clearing (re-reflux).[65] In the present study, the presence of a hiatus hernia had no impact on the patterns of reflux. This suggests that any disruption of the antireflux barrier by a hiatus hernia has no selective effect on the acidity of the refluxate. The presence or absence of a hernia was determined by endoscopy, which may be less sensitive than radiology. It is possible, therefore, that important effects of a hernia were obscured by either a type 2 statistical error or the inclusion of patients with small hernias in the nonhernia group, or both.

In conclusion, ambulatory recordings of gastroesophageal reflux using combined intraluminal impedance and pH monitoring have shown that, compared with controls, patients with reflux disease have a similar total rate of reflux episodes but more acidic refluxates. The air-liquid patterns of reflux support the view that acid reflux is, in part, a consequence of the belch reflex. Contrary to expectations, nonacid reflux does not seem to be a major component of the refluxate, but the potential relevance of this component to symptoms awaits further study. Analysis of patterns of reflux suggests that there are important but as yet poorly characterized differences in the gastric fundic environment that may have a major impact on patterns of acid reflux.

References

1. Johnson LF, Demeester TR. Twenty-four-hour pH monitoring of the distal esophagus. A quantitative measure of gastroesophageal reflux. Am J Gastroenterol 1974;62:325–332.
2. Demeester TR, Johnson LF, Joseph GJ, Toscano MS, Hall AW, Skinner DB. Patterns of gastroesophageal reflux in health and disease. Ann Surg 1976;184:459–470.
3. Dodds WJ, Dent J, Hogan WJ, Helm JF, Hauser R, Patel GK, Egide MS. Mechanisms of gastroesophageal reflux in patients with reflux esophagitis. N Engl J Med 1982;307:1547–1552.
4. Schindlbeck NE, Heinrich C, Konig A, Dendorfer A, Pace F, Muller-Lissner SA. Optimal thresholds, sensitivity, and specificity of long-term pH-metry for the detection of gastroesophageal reflux disease. Gastroenterology 1987;93:85–90.
5. Masclee AA, de Best AC, de Graaf R, Cluysenaer OJ, Jansen JB. Ambulatory 24-hour pH-metry in the diagnosis of gastroesophageal reflux disease. Determination of criteria and relation to endoscopy. Scand J Gastroenterol 1990;25:225–230.
6. McNally E, Kelly J, Ingelfinger F. Mechanism of belching: effect of gastric distension with air. Gastroenterology 1964;46:254–259.
7. Dent J, Dodds WJ, Friedman RH, Sekiguchi T, Hogan WJ, Arndorfer RC, Petrie DJ. Mechanism of gastroesophagal reflux in recumbent asymptomatic subjects. J Clin Invest 1980;65:256–267.
8. Shay SS, Eggli D, Johnson LF. Simultaneous esophageal pH monitoring and scintigraphy during the postprandial period in patients with severe reflux esophagitis. Dig Dis Sci 1991;36: 558–564.
9. Barham C, Gotley D, Miller R, Mills A, Alderson D. Pressure events surrounding oesophageal acid reflux episodes and acid clearance in ambulant healthy volunteers. Gut 1993;34:444–449.
10. Barham CP, Gotley DC, Mills A, Alderson D. Precipitating causes of acid reflux episodes in ambulant patients with gastro-oesophageal reflux disease. Gut 1995;36:505–510.
11. Wyman JB, Dent J, Holloway RH. Changes in oesophageal pH associated with gastro-oesophageal reflux. Are traditional criteria sensitive for detection of reflux? Scand J Gastroenterol 1993; 28:827–832.
12. Sifrim D, Silny J, Holloway RH, Janssens JJ. Patterns of gas and liquid reflux during transient lower oesophageal sphincter relaxation: a study using intraluminal electrical impedance. Gut 1999; 44:47–54.
13. Silny J. Intraluminal multiple electrical impedance procedure for measurement of gastrointestinal motility. J Gastrointest Motil 1991;3:151–162.
14. Silny J, Knigge KP, Fass J, Rau G, Matern S, Schumpelick V. Verification of the intraluminal multiple electrical impedance measurement for the recording of gastrointestinal motility. J Gastrointest Motil 1993;5:107–122.
15. Fass J, Silny J, Braun J, Heindrichs U, Dreuw B, Schumpelick V, Rau G. Measuring esophageal motility with a new intraluminal

impedance device. First clinical results in reflux patients. Scand J Gastroenterol 1994;29:693–702.
16. Skopnik H, Silny J, Heiber O, Schulz J, Rau G, Heimann G. Gastroesophageal reflux in infants: evaluation of a new intraluminal impedance technique. J Pediatr Gastroenterol Nutr 1996; 23:591–598.
17. Sifrim D, Holloway RH, Silny J, Tack J, Lerut T, Janssens J. Composition of the postprandial refluxate in patients with gastroesophageal reflux disease. Am J Gastroent 2001;96:647-655.
18. Orenstein SR, Whitington PF. Positioning for prevention of infant gastroesophageal reflux. J Pediatr 1983;103:534–537.
19. Stanciu C, Bennett JR. Effects of posture on gastro-oesophageal reflux. Digestion 1977;15:104–109.
20. Sontag SJ, O'Connell S, Khandelwal S, Miller T, Nemchausky B, Schnell TG, Serlovsky R. Effect of positions, eating and bronchodilators on gastroesophageal reflux in asthmatics. Dig Dis Sci 1990;35:849–856.
21. Katz LC, Just R, Castell DO. Body position affects recumbent postprandial reflux. J Clin Gastroenterol 1994;18:280–283.
22. Ewer AK, James ME, Tobin JM. Prone and left lateral positioning reduce gastro-oesophageal reflux in preterm infants. Arch Dis Child Fetal Neonatal Ed 1999;81:F201–F205.
23. Khoury RM, Camacho-Lobato L, Katz PO, Mohiuddin MA, Castell DO. Influence of spontaneous sleep positions on nighttime recumbent reflux in patients with gastroesophageal reflux disease. Am J Gastroenterol 1999;94:2069–2073.
24. Little AF, Cox MR, Martin CJ, Dent J. Influence of posture on transient lower oesophageal sphincter relaxation and gastro-oesophageal reflux in the dog. J Gastroenterol Hepatol 1989;4: 49–54.
25. Kapur KC, Trudgill NJ, Riley SA. Mechanisms of gastro-oesophageal reflux in the lateral decubitus positions. Neurogastroenterol Motil 1998;10:517–522.
26. Ireland AC, Dent J, Holloway RH. Preservation of postural control of transient lower oesophageal sphincter relaxations in patients wth reflux esophagitis. Gut 1999;44:313–316.
27. Clark C, Kraus B, Sinclair J, Castell D. Gastroesophageal reflux induced by exercise in healthy volunteers. JAMA 1989;261: 3599–3601.
28. Kraus BB, Sinclair JW, Castell DO. Gastroesophageal reflux in runners. Characteristics and treatment. Ann Intern Med 1990; 112:429–433.
29. Soffer EE, Merchant RK, Duethman G, Launspach J, Gisolfi C, Adrian TE. Effect of graded exercise on esophageal motility and gastroesophageal reflux in trained athletes. Dig Dis Sci 1993; 38:220–224.
30. Yazaki E, Shawdon A, Beasley I, Evans DF. The effect of different types of exercise on gastro-oesophageal reflux. Aust J Sci Med Sport 1996;28:93–96.
31. Peters HP, Wiersma JW, Koerselman J, Akkermans LM, Bol E, Mosterd WL, de Vries WR. The effect of a sports drink on gastroesophageal reflux during a run-bike-run test. Int J Sports Med 2000;21:65–70.
32. Kaye MD. Postprandial gastro-oesophageal reflux in healthy people. Gut 1977;18:709–712.
33. Dodds WJ, Hogan WJ, Helm JF, Dent J. Pathogenesis of reflux esophagitis. Gastroenterology 1981;81:376–394.
34. Dent J, Holloway RH, Toouli J, Dodds WJ. Mechanisms of lower oesophageal sphincter incompetence in patients with symptomatic gastroesophageal reflux. Gut 1988;29:1020–1028.
35. Wiener GJ, Morgan TM, Copper JB, Wu WC, Castell DO, Sinclair JW, Richter JE. Ambulatory 24-hour esophageal pH monitoring. Reproducibility and variability of pH parameters. Dig Dis Sci 1988;33:1127–1133.
36. Weusten BL, Roelofs JM, Akkermans LM, Vanberge-Henegouwen GP, Smout AJ. Objective determination of pH thresholds in the analysis of 24 h ambulatory oesophageal pH monitoring. Eur J Clin Invest 1996;26:151–158.
37. Kahrilas P, Dodds WJ, Dent J, Wyman JB, Hogan WJ, Arndorfer RC. Upper esophageal sphincter function during belching. Gastroenterology 1986;91:133–140.
38. Wyman JB, Dent J, Heddle R, Dodds WJ, Toouli J, Downton J. Control of belching by the lower oesophageal sphincter. Gut 1990;31:639–646.
39. Mittal RK, McCallum RW. Characteristics of transient lower esophageal sphincter relaxation in humans. Am J Physiol 1987; 252:G636–G641.
40. Mittal RK, McCallum RW. Characteristics and frequency of transient relaxations of the lower esophageal sphincter on patients with reflux esophagitis. Gastroenterology 1988;95:593–599.
41. Schoeman MN, Tippett MD, Akkermans LM, Dent J, Holloway RH. Mechanisms of gastroesophageal reflux in ambulant healthy human subjects. Gastroenterology 1995;108:83–91.
42. Penagini R, Schoeman MN, Dent J, Tippett MD, Holloway RH. Motor events underlying gastro-oesophageal reflux in ambulant patients with reflux oesophagitis. J Neurogastroenterol Motil 1996;8:131–141.
43. Stakeberg J, Lehmann A Influence of different intragastric stimuli on triggering of transient lower oesophageal sphincter relaxation in the dog. Neurogastroenterol Motil 1999;11:125–132.
44. Hirschowitz BI. A critical analysis, with appropriate controls, of gastric acid and pepsin secretion in clinical esophagitis. Gastroenterology 1991;101:1149–1158.
45. Collen MJ, Johnson DA, Sheridan MJ. Basal acid output and gastric acid hypersecretion in gastroesophageal reflux disease. Correlation with ranitidine therapy. Dig Dis Sci 1994;39:410–417.
46. Cadiot G, Bruhat A, Rigaud D, Coste T, Vuagnat A, Benyedder Y, Vallot T, Le Guludec D, Mignon M. Multivariate analysis of pathophysiological factors in reflux oesophagitis. Gut 1997;40:167–174.
47. Penagini R, Hebbard G, Horowitz M, Dent J, Bermingham H, Jones K, Holloway RH. Motor function of the proximal stomach and visceral perception in gastro-oesophageal reflux disease. Gut 1998;42:251–257.
48. Zerbib F, des Varannes SB, Ropert A, Lamouliatte H, Quinton A, Galmiche JP. Proximal gastric tone in gastro-oesophageal reflux disease. Eur J Gastroenterol Hepatol 1999;11:511–515.
49. Fletcher J, McColl KE. Oesophageal refluxate acidity is not lowered by meal related intragastric pH buffering (abstr). Gastroenterology 2000;118:A481.
50. Washington N, Steele RJ, Jackson J, et al. Patterns of food and acid reflux in patients with low-grade oesophagitis- the role of an anti-reflux agent. Aliment Pharmacol Ther 1998;12:53–58.
51. Wright JW, Adams V, Gowland PA, Spiller R, Evans D, Mansfield P. Gastric mixing of a solid and liquid meal measured by echo planar magnetic resonance imaging (EPI) (abstr). Gastroenterology 1996;110:A781.
52. Marciani L, Gowland PA, Spiller RC, Manoj P, Moore RJ, Young P, Al-Sahab S, Bush D, Wright J, Fillery-Travis AJ. Gastric response to increased meal viscosity assessed by echo-planar magnetic resonance imaging in humans. J Nutr 2000;130:122–127.
53. Hirschowitz BI. Pepsin and the esophagus.Yale J Biol Med 1999; 72:133–143.
54. Tuttle SG, Ruffin F, Bettarella A. The physiology of heartburn. Ann Intern Med 1961;55:292–300.
55. Breumelhof R, Nadorp JH, Akkermans LM, Smout AJ. Analysis of 24-hour esophageal pressure and pH data in unselected patients with noncardiac chest pain. Gastroenterology 1990;99:1257–1264.
56. Vela M, Camacho-Lobato L, Hatlebakk J, Katz PO, Castell D. Effect of omeprazole (PPI) on ratio of acid to nonacid gastroesophhageal reflux. Studies using simultaneous intraesophageal

impedance and pH measurement (abstr). Gastroenterology 1999;116:A209.
57. Wenzl TG, Silny J, Schenke S, Peschgens T, Heimann G, Skopnik H. Gastroesophageal reflux and respiratory phenomena in infants: status of the intraluminal impedance technique. J Pediatr Gastroenterol Nutr 1999;28:423–428.
58. Weusten BL, Akkermans LM, vanBerge-Henegouwen GP, Smout AJ. Dynamic characteristic of gastro-oesophageal reflux in ambulatory patients with gastro-oesophageal reflux disease and normal control subjects. Scand J Gastroenterol 1995;30:731–737.
59. Sifrim D, Tack J, Lerut T, Janssens J. Transient lower esophageal sphincter relaxations and esophageal body muscular contractile response in reflux esophagitis. Dig Dis Sci 2000;45:1293–1300.
60. Sloan S, Rademaker AW, Kahrilas PJ Determinants of gastroesophageal junction incompetence: hiatal hernia, lower esophageal sphincter, or both? Ann Intern Med 1992;117:977–982.
61. Kahrilas PJ, Lin S, Chen J, Manka M. The effect of hiatus hernia on gastro-oesophageal junction pressure. Gut 1999;44:476–482.
62. Kahrilas PJ, Shi G, Manka M, Joehl RJ. Increased frequency of transient lower esophageal sphincter relaxation induced by gastric distention in reflux patients with hiatal hernia. Gastroenterology 2000;118:688–695.
63. DeMeester TR, Lafontaine E, Joelsson BE, Skinner DB, Ryan JW, O'Sullivan GC, Brunsden BS, Johnson LF. Relationship of a hiatal hernia to the function of the body of the esophagus and the gastroesophageal junction. J Thorac Cardiovasc Surg 1981;82:547–558.
64. Van Herwaarden MA, Samsom M, Smout AJ. Excess gastroesophageal reflux in patients with hiatus hernia is caused by mechanisms other than transient LES relaxations. Gastroenterology 2000;119:1439–1446.
65. Shay SS, Richter JE. Importance of additional reflux events during esophageal acid clearing. Dig Dis Sci 1998;43:95–102.

Received December 19, 2000. Accepted February 21, 2001.
Address requests for reprints to: Daniel Sifrim, M.D., Ph.D., Faculty of Medicine K.U. Leuven, Laboratory G-I Physiopathology, O&N Gasthuisberg, 7th floor, Herestraat 49, 3000, Leuven, Belgium. e-mail: Daniel.Sifrim@med.kuleuven.ac.be; fax: (32) 16-34-5939.
Supported by grants from the F.W.O. and the "Geconcerteerde Onderzoeksactie" of the University of Leuven.

Rokitansky & Aschoff of the Rokitansky–Aschoff Sinuses

Karl von Rokitansky (1804–1878) was born in Königgratz, Bohemia, and was educated first at Prague and then obtained his M.D. degree at Vienna where at age 30 he became professor of pathology and leader of the illustrious triumvirate that included Skoda and von Heber. As a consequence of urging Emperor Joseph II to decree that all Austrian citizens who died would be subject to necropsy, he officiated at nearly 60,000 postmortem examinations, all of which he meticulously described in gracefully composed reports—a record that still stands. By his colleagues he was regarded as a jovial and highly esteemed teacher. In addition to observing in 1842 the cryptic sinuses that mark chronic cholecystitis (redescribed by Aschoff in 1905), he was the first to distinguish lobar and lobular pneumonia, as well as to describe acute yellow atrophy of the liver. He coined the term "spondylolisthesis."

Carl Albert Ludwig Aschoff (1866–1942) was born in Berlin and obtained his M.D. degree at Bonn. He proudly bore duelling scars as evidence of loyalty to his *Burschenshaft* (student fraternity). At Marburg, with his Japanese pupil Sunao Tawara, he described the atrioventricular node and, later at Freiburg, the rheumatoid nodules in the myocardium that became known as "Aschoff bodies." His *Handbook of Pathologic Anatomy* reached its 8th edition in 1935. His death was attributed to bronchial asthma from which he had suffered for many years.

—Contributed by WILLIAM S. HAUBRICH, M.D.
Scripps Clinic and Research Foundation, La Jolla, California

Copyright holder unknown. Photos obtained from the National Library of Medicine website (http://www.nlm.nih.gov).