

Simultaneous Intraesophageal Impedance and pH Measurement of Acid and Nonacid Gastroesophageal Reflux: Effect of Omeprazole

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See editorial on page 1862.

Background & Aims: Nonacid reflux may explain symptoms in acid-suppressed patients. Simultaneous intraesophageal impedance and pH measurement was used to evaluate the frequencies of postprandial acid and nonacid reflux before and after omeprazole administration. **Methods:** Twelve heartburn patients underwent two 2-hour studies of intraesophageal impedance and pH in the right lateral decubitus position after a refluxogenic meal; session 1 without medication, session 2 after 7 days of omeprazole twice daily. Acid and nonacid reflux were quantified. **Results:** Two hundred seventeen reflux episodes were detected before and 261 after omeprazole treatment ($P > 0.05$). Percentage of acid reflux decreased (from 45% to 3%, $P = 0.02$) and nonacid reflux increased (from 55% to 97%, $P = 0.03$) after omeprazole. Heartburn and acid taste were more commonly linked to acid reflux but were also produced by nonacid reflux. Regurgitation was reported equally in acid and nonacid reflux. $\Delta\text{pH} > 1$ did not help predict the presence of symptoms during nonacid reflux. **Conclusions:** During treatment with omeprazole, postprandial reflux becomes predominantly nonacid. Symptoms are more common with acid reflux but are also produced by nonacid reflux. Simultaneous intraesophageal impedance and pH may be useful in evaluating the role of nonacid reflux in symptoms that persist despite adequate acid suppression.

Gastroesophageal reflux disease (GERD) is defined by symptoms or tissue damage resulting from reflux of gastric contents into the esophagus or beyond into the oral cavity or lung. The pathophysiologic role of acid in GERD has been well established by a number of studies in both animals and humans.¹ Ambulatory pH monitoring is currently the best method for detection of acid gastroesophageal reflux.² However, in a number of patients symptoms persist despite adequate acid suppression; it has been suggested that these symptoms may be

secondary to reflux within an alkaline or nonacid pH range, so-called nonacid reflux.³ These observations lend relevance to study of the frequency and contribution of reflux of gastric contents with $\text{pH} > 4$ to symptoms in patients with GERD.

Currently available techniques for the study of nonacid or alkaline reflux include aspiration, scintigraphy, ambulatory pH monitoring, and bilirubin monitoring (Bilitec; Medtronic, Minneapolis, MN).⁴⁻⁸ These methods have limitations. Aspiration studies allow for only short analysis periods, and the accuracy of enzymatic determination of the contents of the aspirates has been questioned.^{1,7,9} Scintigraphic studies are expensive and involve radiation exposure and are usually limited to short monitoring periods.^{1,5,7,9} Ambulatory pH monitoring uses $\text{pH} \geq 7$ as the definition of alkaline reflux, but increased saliva production or bicarbonate secreted by esophageal submucosal glands confounds measurements by increasing esophageal pH in the absence of reflux.^{1,7,9-11} Monitoring with the Bilitec probe is based on the presence of bilirubin and is therefore incapable of measuring bile-free nonacid reflux; furthermore, simultaneous determination of bile and pH in the stomach has been shown to correlate poorly.¹² Additionally, bilirubin monitoring requires a special diet to avoid false-positive readings.^{1,7}

Recently, intraluminal impedance measurement has been introduced as a new technique for the study of bolus movement in hollow organs, such as the esophagus.¹³ Intraluminal impedance has been validated fluoroscopically and manometrically to detect bolus movement along the entire length of the esophagus, both in the oral

Abbreviations used in this paper: GERD, gastroesophageal reflux disease; IE-IMP/pH, intraesophageal impedance and pH; LES, lower esophageal sphincter; SI, symptom index; SSI, symptom sensitivity index.

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and aboral directions.¹⁴ This is done in a pH-independent fashion and thus enables detection of nonacid reflux, including determination of the height reached by the refluxate. Intraluminal impedance has been used in combination with pHmetry to study reflux in infants^{15,16} and patterns of gas and liquid reflux in adults.¹⁷

The aim of our study was to use this technology to assess the frequencies of both acid and nonacid reflux occurring postprandially before and after treatment with a proton pump inhibitor and to evaluate the association between symptoms and reflux episodes of the acid and nonacid types.

Patients and Methods

Patients

The study included 12 patients (5 female and 7 male, mean age 35 years). Patients were eligible if they were between the ages of 18 and 70 years and complained of symptoms compatible with heartburn, occurring at least 3 times weekly. Premenopausal female subjects had pregnancy excluded through a urine pregnancy test. Nursing mothers were excluded from the study. Patients who were taking acid-suppressing or motility agents were asked to stop therapy 1 week before beginning the study.

Methods

The study protocol was approved by the Graduate Hospital Institutional Review Board. On the initial visit, after informed consent was obtained from the patients, a physical examination was performed together with esophageal manometry for determination of lower esophageal sphincter (LES) location. This was followed by 2 additional visits during which simultaneous intraesophageal impedance and pH (IE-IMP/pH) measurement was performed.

On the days of simultaneous IE-IMP/pH measurement, patients came to the laboratory after a fasting period of at least 5 hours. An IE-IMP/pH assembly was used for measurement of acid and nonacid reflux. The 2.1-mm diameter impedance catheter (Sandhill Scientific, Inc.), illustrated in Figure 1, has 14 electrodes, each 4 mm in length, set at 2-cm intervals. Because impedance is measured between adjacent electrodes, this set-up allows for 13 measuring segments. The 2.1-mm diameter pH catheter (Sandhill Scientific, Inc., Highlands

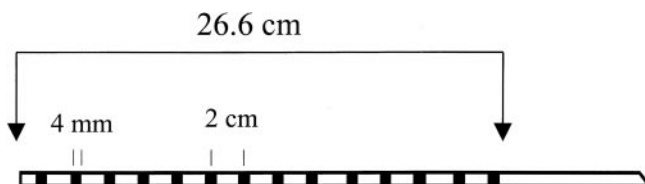


Figure 1. Schematic representation of the impedance catheter with 14 4-mm electrodes set at 2-cm intervals, allowing for 13 impedance measuring segments.

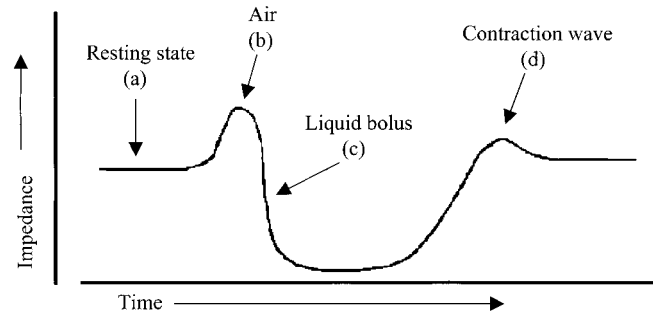


Figure 2. Impedance changes observed during swallowing. The impedance value during the resting state (a) is attributable to the muscle wall surrounding the catheter. At the start of the swallow a small amount of air (b), a poorly conductive material, travels ahead of the liquid bolus and produces an increase in impedance. With the arrival of the liquid bolus at the measuring segment (c), the impedance value decreases. As the liquid bolus leaves the measuring segment, impedance values gradually return to baseline. Before a stable return to the resting state, however, there is an additional increase in impedance to above baseline; this corresponds to the contraction wave (d) that follows the bolus.

Ranch, CO) was tied to the impedance catheter with a 6-0 nylon suture and passed into the esophagus transnasally so that the most distal impedance electrode was positioned 1.5 cm above the LES and pH was recorded in the distal esophagus 5 cm above the proximal margin of the LES. The probes were connected directly to a personal computer that continuously recorded pH and impedance events (Sandhill Scientific, Inc.). Symptom association was evaluated in the last 5 subjects entered in the study. Immediately before the start of each study, patients were asked to alert the investigator (present at all times during recording) of the presence of 1 or more of the following symptoms: heartburn, regurgitation, and acid taste for real-time labeling on the tracing. No attempt was made to quantitate severity of symptoms. Subjects were not reminded to report symptoms once recording began.

Impedance (in ohms) is a measure of the total opposition to current flow between adjacent electrodes. It is inversely proportional to the electrical conductivity and the cross-sectional area of the material through which the current must travel.¹³ The electrical conductivity of the muscular wall, air, and any given bolus material such as food, saliva, or gastric contents is different; thus the presence of each of these substances in the esophageal lumen provides a different impedance pattern. Impedance will decrease if a highly conductive bolus such as saliva reaches the esophagus and increase if a poorly conductive material (air, for example) enters the esophageal lumen.^{13,18-20} The typical impedance changes produced by swallowing are illustrated in Figure 2.

The subjects underwent two 2-hour IE-IMP/pH studies in the right lateral decubitus position. Before each study, they received a refluxogenic meal consisting of a sausage and egg McMuffin (McDonald's; 60% fat) with an 8-oz cup of coffee. The first session was carried out on no medication, and the second session was performed after a 7-day course of omepra-

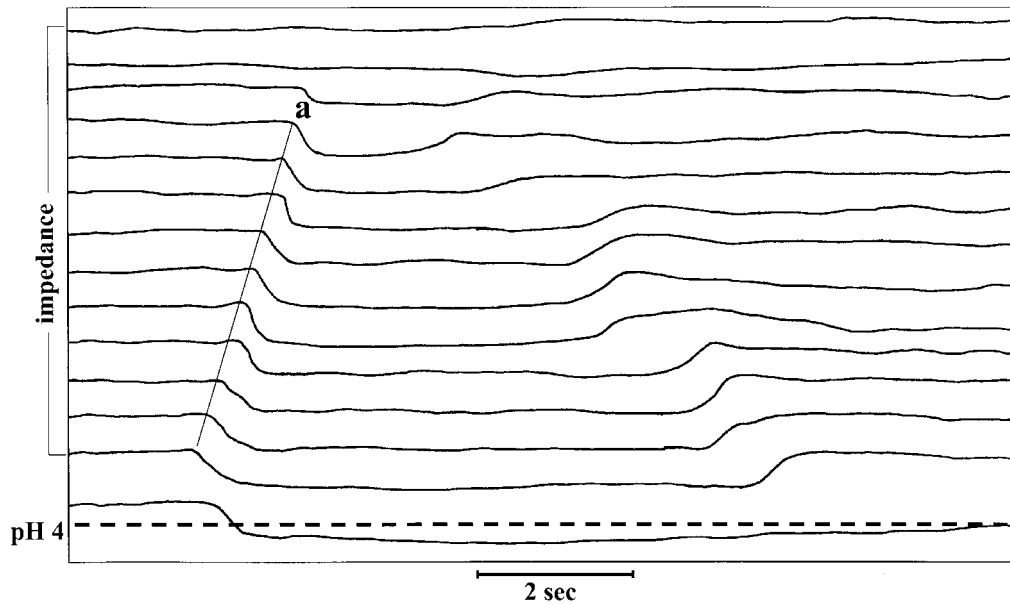


Figure 3. Impedance changes (in ohms) during an acid reflux episode for the 13 measuring segments and pH changes (Y-axis). The *dotted line* marks a pH of 4.0. Point *a* indicates the most proximal level of this impedance pattern of reflux. It is preceded by a sequential decrease in impedance starting at the most distal measurement segment that proceeds toward the proximal esophagus. Arrival of the refluxate into the distal esophagus causes a decrease in pH to <4.0, an acid reflux episode.

zole, 20 mg orally twice daily AC (before breakfast and dinner).

Analysis

All tracings were analyzed manually by 2 separate investigators. Impedance and pH were analyzed independently in search of reflux episodes. Impedance was used to detect reflux of volume, which was considered to occur if there was a

sequential decrease in impedance to a minimum of 50% of baseline value beginning at the most distal recording site and reaching the second most distal recording site (equivalent to 5.5 cm above the LES) or beyond (Figures 3 and 4). Because intraesophageal impedance baseline frequently shifts slightly, the baseline value used to determine a 50% decrease was the average impedance baseline in a 5-second period immediately preceding the reflux episode. The end of the reflux episode was

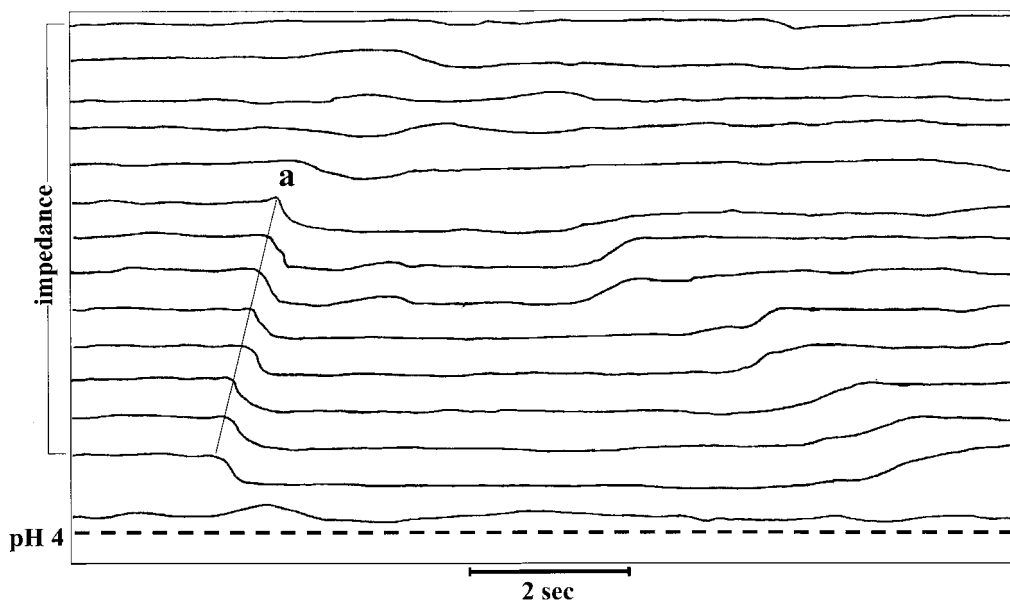


Figure 4. Impedance changes (in ohms) during a nonacid reflux episode for the 13 measuring segments and pH changes (Y-axis). The *dotted line* marks a pH of 4.0. The level of this typical impedance pattern of reflux is indicated by point *a*. This is not accompanied by a decrease in pH to <4.0; thus it is considered an episode of nonacid reflux.

likewise identified when the impedance value returned to more than 50% of baseline value. This endpoint was chosen based on the initial reports using this technique¹³ and was considered sufficiently distinct from baseline shifts to be easily identified.

pH recordings were used to determine the acid or nonacid nature of the refluxate. An acid reflux episode detected simultaneously by impedance and pH was defined as an abrupt decrease in pH to <4.0 for at least 5 seconds occurring within 10 seconds after an impedance-detected reflux event. Reflux was considered nonacid if there was no concomitant decrease in pH to <4.0 during an impedance-detected episode of reflux of volume. pH was also used to determine the presence or absence of a $\Delta\text{pH} > 1$ (decrease in pH of at least 1 unit) for each nonacid reflux episode (i.e., no pH decrease to <4.0).

The height of each reflux episode was determined by the most proximal level at which a $>50\%$ decrease in impedance was detected. Reflux episodes that traveled beyond 13 cm above the LES were considered to be in the proximal esophagus.

The 2 investigators agreed on 95% of reflux. Whenever there was disagreement in the reading of an episode, a consensus was reached between the 2 investigators.

Symptoms were considered associated with reflux, either acid or nonacid, if they occurred in the 2-minute interval immediately after a reflux event. In the rare instance of more than 1 reflux episode occurring within the same 2-minute period before a symptom, only the reflux episode immediately preceding the symptom was considered associated with the symptom. The symptom index (SI) and symptom sensitivity index (SSI) were calculated as $\text{SI} = (\text{Reflux-Related Symptom Events}/\text{Total Symptom Events}) \times 100\%$ and $\text{SSI} = (\text{Reflux-Related Symptom Events}/\text{Total Reflux Episodes}) \times 100\%$.

Statistics were calculated using the GraphPad Software Inc. (San Diego, CA) package of statistical programs. The Mann-Whitney test was used for the comparison of reflux episodes before and after treatment. The Fisher exact test was used to compare acid and nonacid reflux in the first and second postprandial hours, as well as to evaluate symptom association. Significance was established at $P < 0.05$.

Results

Frequencies of Acid and Nonacid Reflux Before and After Treatment

Analysis of all tracings from 2 studies in all patients yielded a total of 478 reflux episodes; 105 of these were acid, 373 were nonacid. Examples of tracings of acid and nonacid reflux episodes are shown in Figures 3 and 4. Of the 105 acid reflux episodes, 2 (1.9%) were detected by pH in the absence of impedance changes; all other acid reflux episodes were detected by both pH and impedance probes.

As shown in Figure 5, 217 reflux episodes occurred before therapy; of these, 98 (45%) were acid and 119 (55%) were nonacid. The total number of reflux episodes

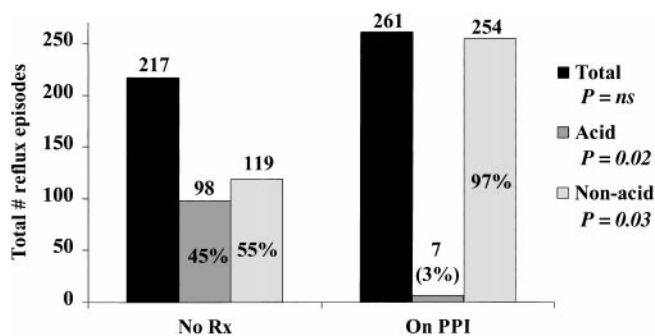


Figure 5. Pooled results of types of total reflux episodes for all 12 subjects before (No Rx) and after (On PPI) treatment with omeprazole. *P* values reflect changes before and after treatment.

increased ($P = \text{NS}$) to 261 during omeprazole treatment; acid reflux episodes decreased to only 7 (3%; $P = 0.02$), and nonacid reflux episodes increased to 254 (97%; $P = 0.03$).

There was a significant difference in the proportion of acid to nonacid reflux in the first and second postprandial hours. Only 17% of reflux episodes were acid in the first postprandial hour; during the second hour, this number increased to 34% ($P < 0.0001$).

We found no significant difference between the median height reached by the refluxate, with 64% of acid reflux episodes and 57% of nonacid episodes reaching the proximal esophagus.

Association of Symptoms With Acid and Nonacid Reflux

We studied symptom association with acid and nonacid reflux in 5 individuals. Heartburn, acid taste, and regurgitation were reported during both acid and nonacid episodes (Figure 6). The presence of any symptom was more common during acid reflux than during nonacid reflux ($P = 0.0005$). When specific symptoms were analyzed separately, we found that heartburn ($P = 0.0001$) and acid taste ($P = 0.003$) were more commonly linked to acid reflux. Regurgitation was reported with similar frequency during acid and nonacid reflux episodes. Only 15 symptom events (11% of the total number of symptoms) were recorded in the absence of either acid or nonacid reflux.

The 5 patients in whom symptoms were recorded generated individually more nonacid reflux (247 episodes) than the initial 7 (126 episodes). Because the technique for recording and analyzing was identical to that used in the initial 7 patients, we considered this a chance occurrence.

Table 1 shows the number of symptomatic acid and nonacid reflux episodes before and after treatment. The 3 columns to the right (HB, AT, RE) show the percentage

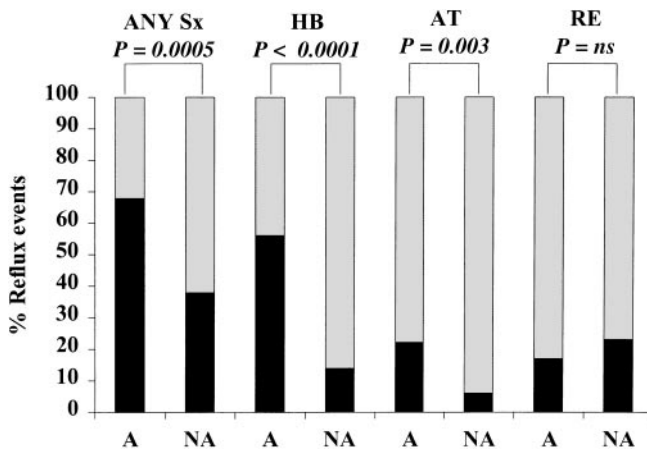


Figure 6. Association between (■, Sx) symptom presence (□, No Sx) or absence and reflux, both acid (A) and nonacid (NA), in the 5 patients in whom symptoms were recorded. HB, heartburn; AT, acid taste; RE, regurgitation.

of symptomatic reflux episodes during which each of these symptoms (heartburn, acid taste, and regurgitation) was reported, either alone or in combination with another symptom. Patients could report 1 or any combination of the 3 symptoms during a single symptom event. As is evident from Table 1, heartburn was frequent during acid reflux, both before and after treatment (84% vs. 67%); regurgitation, although present during acid reflux in the untreated state, was more common after acid suppression (20% vs. 67%).

Heartburn associated with nonacid reflux decreased from 71% before treatment to only 10% after therapy with omeprazole. Conversely, regurgitation reported during nonacid reflux increased from 26% before treatment to 88% after acid suppression.

We calculated SI and SSI before and after treatment, using acid reflux alone (as would be measured with conventional pHmetry) or in combination with nonacid reflux (measurable with IE-IMP/pH). Table 2 shows the pooled SI and SSI for the 5 patients in whom symptoms were recorded. Values above 50% and 10% are considered positive for the SI and SSI, respectively.²¹

Using only acid reflux episodes, the SI was negative both in the untreated state (36%) and after treatment (5%). When nonacid reflux measurements were added to the calculation, the SI became positive, increasing to 87% in the untreated state and 92% after acid suppression with omeprazole.

The following observations regarding the SSI can be derived from Table 2. First, when all reflux episodes (both acid and nonacid) are taken into account, reflux episodes have a higher tendency to be symptomatic in the untreated state (SSI 61%) than during acid-suppression therapy (SSI 31%). Second, acid reflux episodes are likely to produce symptoms, regardless of treatment (SSI 69% and 60% before and after treatment); nonacid reflux episodes, on the other hand, produce fewer symptoms in the treated state (SSI 30%) than before treatment (SSI 57%).

As shown in Table 3, of the 247 nonacid reflux episodes detected in the 5 patients in whom symptom association was evaluated, 94 (38%) episodes produced a $\Delta\text{pH} > 1$. During nonacid reflux, symptoms were more likely ($P = 0.002$) to occur (50%) in the presence of a $\Delta\text{pH} > 1$ than when no pH change occurred (35%); however, only half of symptomatic reflux events were accompanied by a $\Delta\text{pH} > 1$. Thus, $\Delta\text{pH} > 1$ did not reliably predict symptoms during impedance-detected nonacid ($\text{pH} > 4.0$) reflux.

Discussion

In this study of acid and nonacid reflux before and after treatment with omeprazole, patients were evaluated for 2 hours in the right lateral decubitus position after a high-fat meal. These conditions were selected based on our prior studies showing the refluxogenic potential of this meal²² and the strong association between reflux and the right lateral decubitus position.^{23,24} We were able to detect both acid and nonacid reflux episodes with a combined intraesophageal impedance and pH assembly; this is in agreement with the study of Skopnik et al.,¹⁵ in

Table 1. Symptoms Associated With Acid and Nonacid Reflux Before and After Treatment

	GER episodes	GER c Sx	HB (%)	AT (%)	RE (%)
Off Rx					
Acid	36	25	84	36	20
Nonacid	74	42	71	26	26
PPI					
Acid	5	3	67	0	67
Nonacid	173	52	10	10	88

NOTE. Pooled results from 5 patients in whom symptoms were recorded. The columns labeled HB, AT, and RE denote the percentage of symptom events during which heartburn, acid taste, and regurgitation, respectively, were reported. Note that subjects could report 1 or more symptom during a single symptom event (e.g., HB alone or HB + AT). Off Rx, no medication; PPI, on omeprazole treatment; GER, gastroesophageal reflux; Sx, symptoms.

Table 2. SI and SSI Determined Before and After Treatment

	Sx with GER	Total Sx	Total GER	SI (%)	SSI (%)
Acid GER (pHmetry)					
Off Rx	25	77	36	32	69
PPI	3	60	5	5	60
Nonacid GER (IMP/pH)					
Off Rx	42	77	74	55	57
PPI	52	60	173	87	30
Acid + nonacid GER					
Off Rx	67	77	110	87	61
PPI	55	60	178	92	31

NOTE. SI and SSI were determined using acid reflux, nonacid reflux, or all reflux (acid and nonacid). Data represent pooled results from 5 patients in whom symptoms were recorded. Calculation of SI and SSI are described in the text. Off Rx, no medication; PPI, on omeprazole treatment; GER, gastroesophageal reflux; pHmetry, pH measurement only; IMP/pH, combined impedance and pH measurement.

which combined impedance and pH monitoring yielded a large number of nonacid reflux episodes in 17 infants with clinical evidence of gastroesophageal reflux. In another study evaluating the link between reflux and respiratory phenomena in 22 infants, Wenzl et al.¹⁶ found that 78% of reflux episodes causing apnea in this population were nonacid.

Recently, Sifrim et al.¹⁷ used this technique to characterize patterns of gas and liquid reflux during transient LES relaxations in healthy subjects in the sitting position after a refluxogenic meal. They found that 25% of acid reflux episodes were preceded by gas reflux. Contrary to these findings, we detected few episodes of gas reflux. This is probably a consequence of studying patients with full stomachs and in the right lateral decubitus position.²⁵

Our study constitutes the first attempt to quantify acid and nonacid reflux before and after acid suppression with a proton pump inhibitor. The frequencies of acid and nonacid reflux episodes were similar in the untreated state; most acid reflux events occurred during the second postprandial hour. This effect would be expected because of the meal buffering the gastric contents to pH > 4 in the immediate postprandial state. The postmeal timing of our study also explains the frequent occurrence of nonacid reflux despite omeprazole treatment, particularly

in the right lateral decubitus position because of gastric distention.

The total number of postprandial reflux episodes (both acid and nonacid) did not change significantly after acid-suppression treatment. Omeprazole was very effective in controlling acid reflux episodes in this group of patients with heartburn. As shown in our study, reflux continues to occur in the postprandial period during treatment with a proton pump inhibitor but becomes predominantly nonacid. This in turn results in a statistically significant increase in the percentage of nonacid reflux after treatment. In studies using combined bilirubin and pH monitoring, omeprazole significantly decreased not only acid reflux but also bile reflux.²⁶ However, those studies examined bile reflux in a 24-hour period, in contrast to our study, in which 2-hour recordings in the postprandial period were examined. We have yet to determine the effect of omeprazole on nonacid reflux outside of the postprandial period; those studies are currently under way in our laboratory. Furthermore, it is not possible to know whether there was bile in the nonacid reflux episodes detected in our study because the composition of nonacid reflux is not determined by impedance or pH measurements. Because our subjects were studied immediately after a meal, it can be assumed that the nonacid reflux episodes detected were composed mainly of food contents mixed with gastric secretions. This is consistent with studies using simultaneous pH and gamma scintigraphy, which have shown that reflux of neutral materials, undetectable by the pH probe, occurs when gastric contents are buffered by a meal in the postprandial state.²⁷

We recorded symptoms in the last 5 patients enrolled in the study. Our methodology for symptom recording and symptom association differs from that conventionally

Table 3. Relationship of Nonacid Reflux (pH > 4.0) Episodes Detected by Impedance Changes to Symptoms and Δ pH >1.0 or <1.0 in the 5 Patients in Whom Symptoms Were Recorded

	Δ pH > 1	No Δ pH	Total
Symptom present	47	46	93
Symptom absent	47	107	154
Total	94	153	247

reported in 24-hour pHmetry in some aspects. Symptoms were obtained in an intensive monitoring setting and over a short period only in the postprandial state, during which the investigator was present at all times. This situation is quite different from that of a subject pursuing normal daily life activities while carrying an ambulatory pH recorder.

Analysis of symptom correlation showed that heartburn and acid taste occur more commonly in conjunction with acid reflux. Patients also report these symptoms during some nonacid reflux episodes. Although similar numbers of reflux episodes were reported before and after treatment, acid reflux becomes rare once acid is suppressed by medication; nonacid reflux thus becomes responsible for most postprandial reflux symptoms. The predominant symptom accompanying acid reflux in the untreated state was heartburn. After treatment with omeprazole, acid reflux was associated with heartburn and regurgitation with equal frequency. Heartburn, the main symptom accompanying nonacid reflux episodes in the untreated state, is replaced by regurgitation, which becomes the predominant symptom during acid-suppressing therapy.

The following conclusions can be drawn from analysis of the SI and the SSI:

Acid reflux frequently produced symptoms, regardless of whether patients were receiving treatment. However, because many symptoms were produced by nonacid reflux, calculation of the SI using only acid reflux yields a low SI. Adding nonacid reflux episodes to the calculation results in a substantial increase in the SI. Therefore, detection of nonacid reflux, which is beyond the limits of conventional pHmetry but is measurable through IE-IMP/pH, should greatly improve the evaluation of symptom association in treated patients in the postprandial state. Symptoms caused by nonacid reflux, which would be ascribed to non-reflux-related causes or would be deemed functional if only acid reflux were measured, can be determined by IE-IMP/pH.

When the importance of $\Delta\text{pH} > 1$ during nonacid reflux was evaluated, it was found that this measurement was not useful in that only half of symptoms occurred in the presence of $\Delta\text{pH} > 1$ and, conversely, only half of episodes in which there was a $\Delta\text{pH} > 1$ produced a symptom (Table 1). Therefore, presence of a $\Delta\text{pH} > 1$ did not help predict the presence of symptoms.

Other investigators have suggested that "nontraditional" decreases in pH may indicate acid reflux when esophageal pH remains >4.0 but has an abrupt decrease of at least 1 pH unit (i.e., $\Delta\text{pH} > 1$).^{17,21} It can be assumed that some acid has traveled into the esophagus

if the reflux of volume, as detected by impedance, is accompanied by a $\Delta\text{pH} > 1$, even when pH does not reach levels below 4.0. However, a pH of 4.0 is generally accepted as the optimal threshold for defining pathologic reflux during esophageal pH monitoring,^{28,29} and mucosal injury was detected in animal studies only when acid exposure to pH < 4.0 was achieved.³⁰ The precise meaning and importance of relative decreases in pH remains to be determined.

Although our observations on symptom correlation are based on a small number of patients, they help support the feasibility of studying symptom association with both acid and nonacid reflux using combined IE-IMP/pH. Our observations relate specifically to conditions conducive to reflux (i.e., lying on the right side after a refluxogenic meal). These observations cannot be extrapolated outside of the monitoring period. Once ambulatory monitoring becomes possible, it will allow recording of the effect of proton pump inhibitors on nonacid reflux and their relationship to symptoms outside of the postprandial period and in different body positions.

In summary, we found that combined IE-IMP/pH measurement detects both acid and nonacid gastroesophageal reflux. Our observations are limited to postprandial reflux patterns, but they do document a striking decrease in the amount of acid reflux after therapy with omeprazole, with continuing postprandial regurgitation of nonacid gastric contents. Given its ability to detect nonacid reflux, this technique can be useful in elucidating the role of nonacid reflux in the persistence of reflux symptoms in patients who have received adequate acid suppression.

References

1. Vaezi MF, Singh S, Richter JE. Role of acid and duodenogastric reflux in esophageal mucosal injury: a review of animal and human studies. *Gastroenterology* 1995;108:1897-1907.
2. DeVault KR, Castell DO. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. *Am J Gastroenterol* 1999;94:1434-1442.
3. Navaratnam RM, Winslet MC. Gastro-oesophageal reflux: the disease of the millennium. *Hosp Med* 1998;59:646-649.
4. Stein HJ, Feussner H, Kauer W, DeMeester TR, Siewert JR. Alkaline gastroesophageal reflux: assessment by ambulatory esophageal aspiration and pH monitoring. *Am J Surg* 1994;167:163-168.
5. Velasco N, Pope CE, Gannan RM, Roberts P, Hill LD. Measurement of esophageal reflux by scintigraphy. *Dig Dis Sci* 1984;29:977-982.
6. Iftikhar SY, Ledingham S, Evans DF, Yusuf SW, Steele RJC, Atkinson M, Hardcastle JD. Alkaline gastro-oesophageal reflux: dual probe pH monitoring. *Gut* 1995;37:465-470.
7. Vaezi MF, Richter JE. Importance of duodeno-gastro-esophageal reflux in the medical outpatient practice. *Hepatogastroenterology* 1999;46:40-47.
8. Stein HJ, Kauer WKH, Feussner H, Siewert JR. Bile acids as components of the duodenogastric refluxate: detection, relation-

- ship to bilirubin, mechanism of injury, and clinical relevance. *Hepatology* 1999;46:66–73.
9. Girelli CM, Cuvello P, Limido E, Rocca F. Duodenogastric reflux: an update. *Am J Gastroenterol* 1996;91:648–653.
 10. DeVault KR, Georgeson S, Castell DO. Salivary stimulation mimics esophageal exposure to refluxed duodenal contents. *Am J Gastroenterol* 1993;88:1040–1043.
 11. Singh S, Bradley LA, Richter JE. Determinants of oesophageal “alkaline” pH environment in controls and patients with gastroesophageal reflux disease. *Gut* 1993;34:309–316.
 12. Just RJ, Leite LP, Castell DO. Changes in overnight fasting intragastric pH show poor correlation with duodenogastric bile reflux in normal subjects. *Am J Gastroenterol* 1996;91:1567–1570.
 13. Silny J. Intraluminal multiple electric 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. 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.
 16. 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.
 17. 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.
 18. 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.
 19. Nguyen HN, Silny J, Matern S. Multiple intraluminal impedance for recording of upper gastrointestinal motility: current results and further implications. *Am J Gastroenterol* 1999;94:306–317.
 20. Nguyen HN, Silny J, Albers D, Roeb E, Gartung C, Rau G, Matern S. Dynamics of esophageal bolus transport in healthy subjects studied using multiple intraluminal impedance. *Am J Physiol* 1997;273:G958–G964.
 21. Smout AJPM. Ambulatory monitoring of esophageal pH and pressure. In: Castell DO, Richter JE, eds. *The esophagus*. 3rd edition. Philadelphia: Lippincott Williams & Wilkins, 1999:119–133.
 22. Becker DJ, Sinclair J, Castell DO, Wu WC. A comparison of high and low fat meals on postprandial esophageal acid exposure. *Am J Gastroenterol* 1989;84:782–786.
 23. Katz LC, Just R, Castell DO. Body position affects recumbent postprandial reflux. *J Clin Gastroenterol* 1994;18:280–283.
 24. 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.
 25. Shay SS, Conwell DL, Mehindru V, Hertz B. The effect of posture on gastroesophageal reflux event frequency and composition during fasting. *Dig Dis Sci* 1996;41:505–511.
 26. Champion G, Richter JE, Vaezi MF, Sing S, Alexander R. Duodenogastric reflux: relationship to pH and importance in Barrett’s esophagus. *Gastroenterology* 1994;107:747–754.
 27. Washington N, Steele RJC, Jackson SJ, Washington C, Bush D. Patterns of food and acid reflux with low-grade esophagitis B the role of an anti-reflux agent. *Aliment Pharmacol Ther* 1998;12:53–58.
 28. 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.
 29. Schindlbeck NE, Ippisch H, Klauser AG, Muller-Lissner SA. Which pH threshold is best in esophageal pH monitoring? *Am J Gastroenterol* 1991;86:1138–1141.
 30. Pursnani KG, Mohiuddin MA, Geisinger KR, Weinbaum G, Katzka DA, Castell DO. Experimental study of acid burden and acute esophagitis. *Br J Surg* 1998;85:677–680.

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