Digestive Diseases and Sciences, Vol. 50, No. 9 (September 2005), pp. 1584–1590 (© 2005)
DOI: 10.1007/s10620-005-2901-5

Direct Comparison of Impedance, Manometry, and pH Probe in Detecting Reflux Before and After a Meal

STEVEN SHAY, MD, and JOEL RICHTER, MD

Combining GERD tests allows strengths and weaknesses of each method to be identified in detecting and characterizing reflux (RE). Aim of this study was to compare two methods that measure bolus volume of a refluxant (impedance monitoring (Imp) and manometry (common cavity)) to pH monitoring which measures changes in acid concentration of a refluxant. Nineteen symptomatic GERD patients and 10 normal volunteers were studied before and after a meal. All had 2-hr simultaneous manometry, pH, and Imp (six sites: 3, 5, 7, 9, 15, 17 cm above LES). Reflux by pH was a fall in pH from above to below 4. There were 973 RE's in all subjects, but only 19% were detected simultaneously by all three methods. Imp detected more RE's (96%) than manometry (76%) or pH probe (28%). Imp was the only method to detect 15% (144/973) of RE's, while detection only by pH probe (2%) or manometry (2%) was rare. Most RE's detected by Imp were detected simultaneously by manometry (75%,720/937). Those not detected by manometry were usually in blind spots either in the vulnerable period 2–3 sec after a swallow, during a posture change, or during a Valsalva. Most RE's detected by Imp were not detected by the pH probe. Though most liquid RE's fasting were detected by pH, most liquid postprandial RE's were not, due primarily to weakly acidic rather than superimposed acid RE's. Bolus clearing time by Imp and manometry was nearly identical, while acid clearing was threefold longer than bolus clearing by Imp or manometry. In conclusion, impedance monitoring is better than manometry and pH monitoring in RE detection before and after a meal, and manometry in determining RE composition as liquid or gas. The pH probe measures RE acidity and acid clearing. Simultaneous impedance and pH combines the two methods strengths, and is a powerful tool for reflux detection and characterization.

KEY WORDS: impedance monitoring; pH monitoring; esophageal manometry; GERD.

Accurate determination of gastroesophageal reflux frequency is important in assessing the competency of the antireflux barrier and correlation of reflux with symptoms. However, GERD tests detect reflux differently. The pH probe, the traditional "gold standard," defines reflux as a pH fall from above to below 4; i.e., a change in acid concentration no matter whether the volume of refluxant is 1 or 1000 cc. (1) In contrast to the pH probe, manometry and impedance monitoring detect reflux based on refluxant volume.

Manometry has been used as a reflux test. Scintigraphy, performed simultaneous with manometry and pH, confirmed that manometry detected postprandial reflux of radiolabelled gastric contents when an intraesophageal pressure increase occurred, the increased intraesophageal pressure persisted as the radiolabelled gastric contents remained in the esophagus, and reluxant cleared as intraesophageal pressure decreased to baseline with a primary or secondary esophageal contraction (2). Reflux by manometry has been used simultaneous with pH to

Manuscript received May 28, 2004; accepted January 18, 2005.
From the Department of Gastroenterology, Cleveland Clinic Foundation, Cleveland, Ohio, USA.
Address for reprint requests: Steven S. Shay, MD, Desk A30, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Ohio 44195, USA; shays@ccf.org.

identify nonacid reflux with pH > 4 (3–5), as well as superimposed acid reflux occurring with pH < 4 during the acid clearing interval after an acid reflux event (4, 5). In fact, simultaneous manometry and pH monitoring allowed superimposed acid reflux to be identified as the main cause of daytime prolonged acid exposure rather than poor clearance (6).

Impedance monitoring (Imp) detects a bolus when resistance to current flow changes as the bolus bridges an electrode pair. Imp detects gastroesophageal reflux when bolus transit is retrograde in two or more electrode pairs placed at intervals in the esophagus. It can also distinguish boluses with different composition, since a liquid bolus decreases impedance while a gas bolus increases resistance (7).

This study aims to identify in a head-to-head comparison the strengths and weaknesses of these three methods in reflux detection and their clearing. This is done by simultaneous monitoring with all three methods before and after a meal, when reflux is most common.

METHODS

Study Population. There were 29 (M/F—13:16) study subjects spanning the spectrum of reflux disease. Ten were normal volunteers without any symptoms of gastroesophageal reflux. Nineteen had symptomatic GERD, 9/19 with normal endoscopy but abnormal 24 hr pH (total acid exposure >5.5%), and 10/19 with two or more esophageal erosions/ulcerations and/or Barrett's esophagus.

Study Design. All study subjects underwent 2-hr simultaneous manometry, pH, and Imp in three identical intervals of 40-min each (see Figure 1). One 40-min interval was fasting, and two 40-min intervals without interruption were after a standard meal comprised of a turkey pita sandwich and Gatorade (300 cc). Each 40-min interval was first in the left and right recumbent (10 min each) posture, and then in the upright posture (20 min).

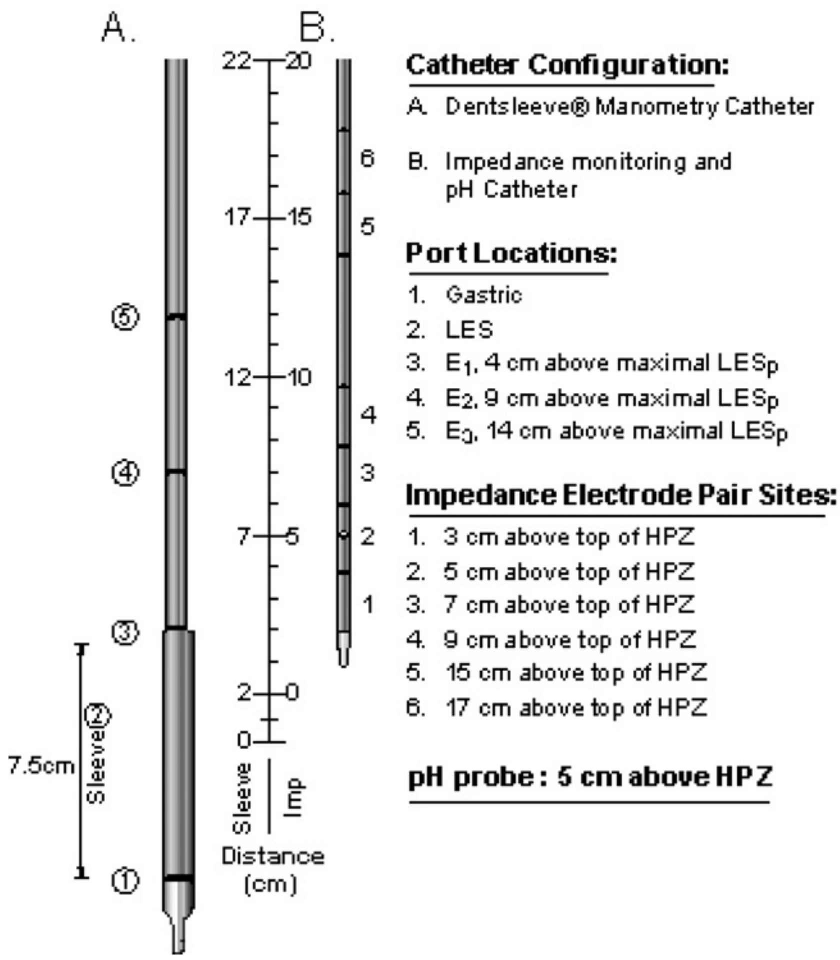


Fig 1. Study schedule and catheter configuration. Note locations of perfusion ports for manometry, electrode pair sites for impedance monitoring (Imp), and pH probe. LES, lower esophageal sphincter.

P1: KEG
sjny355-ddas-502901 DDAS.cls August 10, 2005 23:57

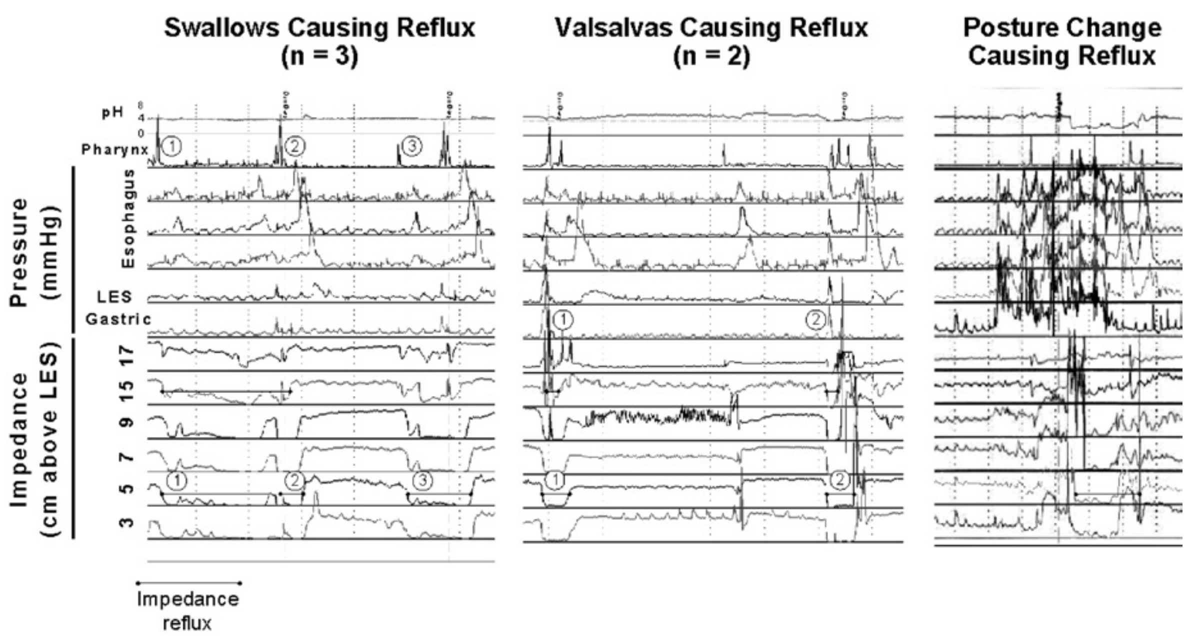


Fig 2. Examples of reflux by impedance (Imp) but not manometry during simultaneous manometry-Imp-pH. (A) Three "weakly acidic" liquid reflux events detected by Imp occur after swallows (see pharynx swallow marker) and reach the 15 cm Imp site. (B) Two "weakly acidic" liquid reflux events detected by Imp occur during Valsalva maneuvers (see pressure spike at all pressure sites) and reach the 17 cm Imp site. (C) A liquid acid reflux events detected by Imp occurs during a posture change, and reaches the 9 cm Imp site. Reflux in (A) and (B) was recognized by the patient as regurgitation.

The subjects were studied in accordance with protocol #4563, which was approved by the Institutional Review Board on September 27, 2001 at the Cleveland Clinic Foundation. Written informed consent was obtained.

Simultaneous Esophageal Manometry, Imp, and pH Monitoring. A multichannel esophageal manometry catheter with a distal sleeve (7 cm; DentSleeve) was passed through the nose and into the esophagus so that it straddled the LES (Figure 1). A 2.13-mm Imp-pH catheter (Sandhill Z-TC) was passed adjacent to the manometry catheter such that the perfused side ports and Imp sites had the configuration as in Figure 1. Swallows were recorded by an air-perfused hypopharyngeal port. All data was recorded simultaneously by Sandhill Insight data acquisition system for subsequent analysis.

Definition of Reflux and Clearing (Figures 2 and 3). Manometry defined a reflux event when a common cavity occurred. A common cavity (8) was defined as an increase in intraesophageal pressure of $\geq$4 mmHg from gastroesophageal pressure equilibration, and not associated with increased intraesophageal pressure from a swallow, dysmotility, or movement. Its duration was seconds until onset of a primary or secondary peristaltic contraction that decreased intraesophageal pressure to baseline.

Impedance channels were examined for reflux. A liquid reflux event was defined by impedance when a fall in ohms $\geq$50% from baseline occurred in at least the two distal channels in an aboral direction, and for $\geq$2 sec in the distal channel (9). Its clearing time was time until return to the impedance level denoting reflux onset at the Imp site 5 cm above the LES. A gas reflux event was defined by impedance when a simultaneous or near-simultaneous rise $\geq$50% in impedance from baseline occurred in at least two consecutive channels. The distal channels did not need to be involved in gas reflux.

The pH probe defined acid reflux traditionally; i.e., a fall in pH from above to below 4, and acid clearing time was seconds until pH 4 was again achieved. However, there were many occasions when the pH probe did not detect reflux, but impedance monitoring or manometry detected reflux. When this occurred, reflux subcategories were defined as recently proposed by the Consensus Conference for Detection and Definitions of Acid, Nonacid, and Gas Reflux, an international workshop held in Porto, Portugal November 2002 (10). "Superimposed acid reflux" was defined as reflux while pH is $<$4 during acid clearing. "Weakly acidic" reflux was defined as pH nadir $\geq$4 but $<$7 during reflux; i.e., acid is present, but in concentrations $\leq$12 meq HCl/L. "Weakly alkaline" was defined as no acid present as intraesophageal pH increases to $\geq$7 or remains $\geq$7 during reflux (0 meq HCl/L).

Statistical Analysis

The data is presented as frequencies and percentages for categorical variables and means for continuous variables. McNemars test for paired proportions compared results from the three methods.

RESULTS

Reflux Detection by the Three Methods. Impedance monitoring detected more reflux (96%, 937/973) than either manometry (76%, 740/973), pH probe (28%, 274/973), or both manometry and pH probe (all $p < .001$)

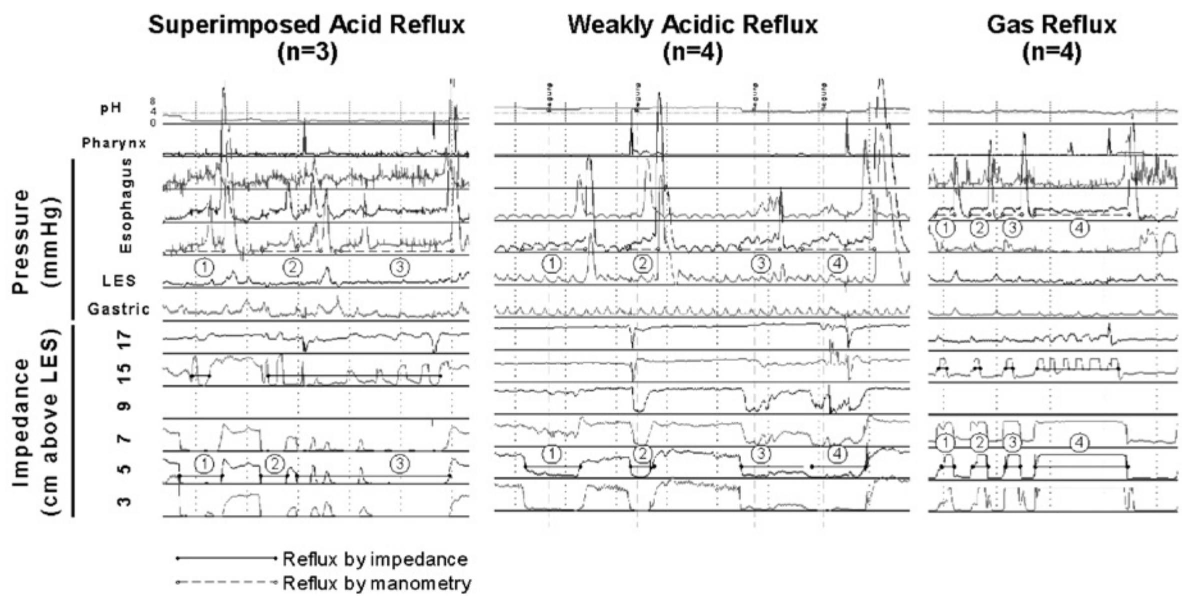


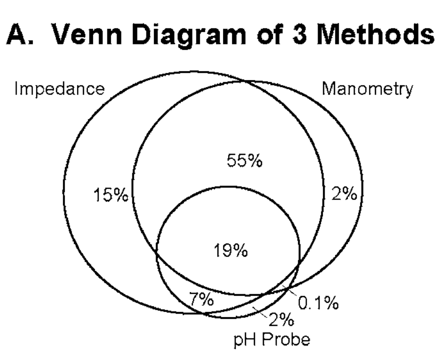
Fig 3. Examples of reflux by impedance (Imp) and manometry but not pH probe during simultaneous manometry-Imp-pH. (A) Three "superimposed acid" liquid RE's detected by Imp and manometry (see 1–3) occur while pH is already <4 from previous acid reflux (no shown), and they reach the 15 cm Imp site. (B) Four "weakly acidic" liquid RE's detected by Imp and manometry (see 1–4) occur as pH is ≥4 but <7, and two reach the 9 cm Imp site. The patient recognizes them as regurgitation (C) Four gas-only RE's are detected by Imp (note the dramatic impedance increase) and manometry while pH is >4, and all reach the 15 cm Imp site.

(Figure 4). Only 19% were detected by all three methods simultaneously. Impedance fall for liquid reflux was a median of 1300 Ω to a median of 300 Ω, and impedance increase with gas-only reflux was a median of 1900 Ω to a median of ≥12,000 Ω.

Most reflux by Imp was detected simultaneously by another method (Figure 2), but 15% were detected only by Imp. Reflux detection only by manometry or the pH probe was rare (each 2%).

Reflux Detection by Impedance Monitoring, but Not Manometry (Figure 2). Most reflux (75%, 720/937) detected by Imp was simultaneously detected by manometry. Three causes were responsible for 68% (148/217) of RE's detected by Imp but not manometry: 1) reflux during the vulnerable period 2–3 sec after a swallow (40%); 2) reflux during a change in posture (19%); and 3) reflux induced by a voluntary abdominal strain (Valsalva maneuver, 9%). Less commonly, there was a minimal (or no) increase in intraesophageal pressure that did not meet the threshold of 4 mm for a common cavity, or a tertiary wave with pressure >15 mmHg that occurred simultaneous with reflux detected by Imp.

Reflux Detection by Impedance Monitoring, But Not the pH Probe. Most reflux detected by Imp was not detected by the pH probe in the entire 2-hr study. However, there were two factors responsible for this (see Table 1, Figure 3): 1) whether reflux was postprandial or fasting, and 2) reflux composition. Most postprandial liquid reflux



B. Reflux detected by:

Impedance+Manometry	535
Impedance+Manometry+pH	184
Impedance alone	144
Impedance+pH	74
Manometry alone	20
pH alone	15
Manometry+pH	1
Total	973

Fig 4. Reflux detection by manometry, impedance, and pH monitoring.

TABLE 1. COMPOSITION AND ACIDITY OF REFLUX 40-MIN FASTING VS. TWO 40-MIN POSTPRANDIAL INTERVALS

	Fasting		*1st Postprandial*		*2nd Postprandial*	
	N	*Total RE (%)*	N	*Total RE (%)*	N	*Total RE (%)*
Total RE's for interval	241	100	435	100	277	100
Composition by impedance						
Liquid reflux						
Acid (detected by pH)	43	18	135	31	89	32
Not detected by pH	12		155		119	
Superimposed acid	10	4	35	8	35	13
Weakly acidic	2	1	120	28	84	30
Weakly alkaline	0	0	0	0	3	1
Gas-only reflux	186	77	145	33	66	24

(55%) was not detected by pH. These reflux episodes were threefold more commonly weakly acidic than superimposed acid reflux. In contrast, fasting liquid reflux was usually (78%) detected by pH, and when liquid reflux was not detected by pH, most was superimposed acid reflux while weakly acidic reflux was rare.

Weakly alkaline liquid reflux was very rare. In fact, it occurred only three times in the entire study population.

Gas-only reflux by Imp without a pH fall to below 4 was very common, even more frequent (1.2-fold; 364:299) than liquid reflux by Imp without a pH fall to below 4. Thus, reflux composition was also important in reflux being detected by impedance but not pH.

Small pH changes occurred with 55% of liquid reflux not detected by the pH probe, either superimposed acid reflux, weakly acidic, or weakly alkaline. A pH fall $\geq$1 pH Unit was detected with 30% (90/299), and a pH fall $<$1 U but $\geq$.5 U with 25% (76/299).

Composition of Reflux Detected by the pH Probe. Reflux detected by the pH probe and Imp was predominantly liquid. However, 8% (22/274) met the criteria for gas-only.

Reflux Clearing by the Three Methods (Table 2). Reflux clearing was nearly identical for reflux episodes detected by both impedance and manometry. However, acid clearing was threefold longer than bolus volume clearing for reflux detected by pH and impedance or pH and manometry.

DISCUSSION

This study found different reflux detection rates for impedance monitoring, pH monitoring, and manometry. Since no single method detected every reflux episode, none can be proposed as a true "gold standard." However, the best single test was Imp, which detected 96% of all reflux episodes, and in 15% was the only method to detect reflux.

The two "volume" tests, impedance monitoring and manometry, usually agreed in reflux detection and clearing time. However, this study shows that impedance is clearly a better test for detecting reflux. First, Imp doesn't have "blind spots" as manometry does. Common cavities can't be detected when intraesophageal pressure is already increased by 1) swallowing a bolus (i.e. the intrabolus pressure, which is present for 2–5 sec until the peristaltic contraction reaches the distal esophagus), 2) during voluntary Valsalva maneuvers, or 3) during movement such as a change in posture. Second, impedance can detect reflux composition, and distinguish more important liquid boluses from gas-only boluses. Third, Imp reflux is easier to detect than a common cavity in most GERD patients and normal subjects. This is because falls and rises in impedance were fourfold and sixfold for liquid and gas respectively, while intraesophageal pressure increases may be difficult to discern, especially when pressure tracings are being reviewed at 0–50 mmHg ranges. Fourth, Imp can detect boluses as small as 1 cc (11), while manometry requires enough refluxant to raise intraesophageal pressure. Fifth, technical advantages of Imp vs manometry include the ability to place electrode pairs at any desired site (e.g., esophageal, hypopharyngeal) on currently available pH electrodes with a 2.1 mm o.d., and no need for fluid perfusion.

TABLE 2. COMPARING REFLUX EVENT CLEARING BY THREE METHODS

	Clearing (sec)			
Detected by	*Imp*	*Manometry*	*pH*	p *Value*
Imp and manometry (n = 719)	18 ± 1	19 ± 1	NA	0.7
Imp and pH probe (n = 258)	21 ± 1	NA	58 ± 6	.001
pH prove and manometry (n = 185)	NA	23 ± 1	58 ± 6	.001

Note. Imp = impedance. Mean ± SEM.

Impedance detected threefold more reflux episodes than the pH probe. This was primarily a result of whether liquid reflux was fasting or postprandial, but was also due to gas-only reflux as discussed later. While fasting, when gastric contents are acidified, liquid reflux was usually detected by the pH probe, and nearly all not detected by pH were superimposed acid reflux detected during an acid clearing interval. If more of the study had been done fasting before the meal or fasting while asleep, the pH probe would have detected substantially more liquid reflux. However, the focus of this report was to maximize reflux frequency so all three methods could be compared to each other, and fasting liquid reflux was threefold and twofold less frequent than liquid reflux in the 1st and 2nd postprandial periods, respectively.

In contrast to fasting, only 45% of postprandial liquid reflux was detected by the pH probe. This was primarily due to gastric neutralization, as liquid reflux not detected by pH was threefold more commonly weakly acidic than superimposed acid reflux. Expanding pH criteria for reflux should increase detection of reflux by the pH probe alone. We found that expanding pH to include a >1 Unit fall from any pH did decrease missed liquid reflux by 30%, and expanding criteria to $\geq .5$ Units decreased missed liquid reflux by 55%. However, the sensitivity and specificity of small pH falls is unknown. Rather than expanding pH criteria to detect weakly acidic reflux, combining impedance and pH monitoring allows for their accurate detection. Some symptoms (e.g. regurgitation and chest pain) are commonly experienced postprandial when weakly acidic reflux is common, and a recent study found that symptom index was converted from negative to positive only by adding nonacid reflux events detected by impedance to acid reflux events detected by the pH probe (9). Thus, the symptom index should improve with 24-hr Imp-pH off therapy. However, we expect the main role of 24-hr Imp-pH to be in persistently symptomatic patients despite adequate PPI therapy, when adequacy of acid suppression, reflux frequency, and symptom association with weakly acidic reflux can be simultaneously assessed. In a preliminary report of 63 of these patients, 19/63 (30%) of all patients and 19/47 (40%) of patients who had their typical symptoms and pushed the symptom button on the study day had only abnormal nonacid reflux event frequency and/or positive symptom index with nonacid reflux since their total acid expposure was $<1.6\%$ confirming adequate acid suppression. However, outcome data was not presented (12).

Gas-only reflux by impedance without a pH fall to <4 was very common, even more common than liquid reflux by impedance without a pH fall to <4. This was the second reason the pH probe failed to detect reflux detected by impedance. Gas-only reflux occurred most commonly fasting, presumably due to gas without liquid at the EG junction when integrity of the antireflux barrier was breached. Presumably gas-only reflux is pathophysiologically unimportant because it contains no damaging component.

Acid clearing was threefold longer than volume clearing for two reasons. First, the two-step process of acid clearing requires not only clearing of the majority of an acid bolus (first step), but also neutralization by saliva of the small residue that remains after volume clearing (second step; (13)). Neither manometry or impedance is sufficiently sensitive to detect the small acid residue in the second step of acid clearing. As a result, the pH probe has an unmatched advantage in measurement of the most important clinical parameter of reflux, acid exposure. Second, superimposed acid reflux during the acid clearing interval also prolonged acid clearing as has been previously reported (6, 14).

Though impedance monitoring is the best test for reflux event detection, it has limitations. First, tracings with a low baseline impedance, typically found in patients with severe esophagitis or Barrett's esophagus (15) are difficult to interpret, though they can usually be interpreted by those experienced in reading impedance tracings. Second, this study also shows detecting composition is not perfect, since 5% of gas-only reflux had a pH fall from above to below 4. This is likely due to a small volume of liquid present that is below the detection threshold in the predominantly gas refluxant, and is supported by their very fast acid clearance in a median of 12 sec. Third, automated analysis for prolonged monitoring has been developed, but accuracy needs to be further improved and assessed, especially when a low baseline is present.

This report has limitations beyond those of measuring impedance. First, we have combined patient populations and normal volunteers. This was done for this report which is focused on reflux test comparison. A separate report comparing in the three populations the mechanisms of reflux, and the effect of a meal and posture on reflux has been presented in preliminary form (16). Second, our study is done with a specific catheter and reflux definitions, and may not apply to other catheter configurations and reflux definitions.

In summary, these findings support consensus conclusions of an international panel of 11 experts at the Porto Consensus Conference on Acid, Nonacid, and Gas Reflux that impedance monitoring is the only recording method that can achieve high sensitivity for detection of all types of reflux episodes. Furthermore, combining impedance and pH monitoring allows detection of all reflux events and gives the best possible evaluation of the antireflux barrier (10). However, clinical studies and outcome data will ultimately define the use of combined impedance and pH monitoring in patients with GERD or suspected GERD.

REFERENCES

1. Johnson LF, DeMeester TR: Twenty-four hour pH monitoring of the distal esophagus. A quantitative measure of gastroesophageal reflux. Am J Gastroenterol 62:325–332, 1974
2. Shay S, Eggli D, Johnson L: Simultaneous esophageal pH monitoring and scintigraphy during the postprandial period in patients with severe reflux esophagitis. Dig Dis Sci 36:558–564, 1991
3. 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 44:47–54, 1999
4. Shay S, Bomeli S, Richter J: Multichannel intraluminal impedance accurately detects fasting, recumbent reflux events and their clearing. Am J Physiol Gastrointest Liver Physiol 283:G376–G383, 2002
5. Wyman J, Dent J, Holloway R: Changes in oesophageal pH associated with gastro-oesophageal reflux. Are traditional criteria sensitive for detection of reflux? Scand J Gastroenterol 28:827–832, 1993
6. Shay S, Richter J: Importance of additional reflux events during esophageal acid clearing. Dig Dis Sci 43:95–102, 1998
7. Silny J: Intraluminal multiple electric impedance procedure for measurement of gastrointestinal motility. J Gastrointest Motil 3:151–162, 1991
8. Butterfield D, Struthers JE, Showalter J: A test of gastroesophageal sphincter incompetence: The common cavity test. Dig Dis Sci 5:415–421, 1972
9. Vela M, Camacho-Lobato L, Srinivasan R, Tutuian R, Katz PO, Castell DO: Simultaneous intraesophageal impedance and pH measurement of acid and nonacid gastroesophageal reflux: Effect of Omeprazole. Gastroenterology 120:1599–1606, 2001
10. Sifrim D, Castell D, Dent J, Kahrilas P: Gastro-esophageal reflux monitoring: Review and consensus report on detection and definitions of acid, non-acid, and gas reflux. Gut 53:1024–1031, 2004
11. Srinivasan R, Vela M, Katz P, Castell D: Multichannel intraluminal impedance (MII): A highly sensitive technique to detect small intraesophageal volumes. Gastroenterology A-489, 2000
12. Shay S, Sifrim D, Tutuian R, Vela M, Zhjang X, Castell D: Multichannel intraluminal impedance in the evaluation of patients with persistent GERD symptoms despite bid proton pump inhibitors: A multicenter study. Gastroenterol 126:A-324, 2004
13. Helm JF, Dodds WJ, Pelc LR, Palmer DW, Hogan WJ, Teeter BC: Effect of esophageal emptying and saliva on clearance of acid from the esophagus. N Engl J Med 310:284–288, 1984
14. Shay S, Johnson L, Richter J: Acid rereflux: A review, emphasizing detection by impedance, manometry, and scintigraphy, and the impact on acid clearing pathophysioilogy as well as interpreting the pH record. Dig Dis Sci 48:1–9, 2003
15. Sifrim D, Holloway RH, Tack J, Silny J, Lerut A, Janssens J: Impedance patterns at the gastroesophageal junction and distal esophagus in patients with Barrett's esophagus. Gastroenterology 118:A-488, 2000
16. Shay S, Richter J: GERD populations distinguished by short-term simultaneous manometry, pH monitoring, and multichannel intraluminal impedance. Gastroenterology 124:A-416, 2003.