

# Ambulatory pH Monitoring: New Advances and Indications

Brant Lutsi, MD, Ikuo Hirano, MD

Dr. Hirano is Associate Professor of Medicine and Dr. Lutsi is a gastroenterology fellow, both at the Northwestern University Feinberg School of Medicine in Chicago, Ill.

Address correspondence to:  
Ikuo Hirano, MD, Division of Gastroenterology and Hepatology, Northwestern University Feinberg School of Medicine, 676 North St Clair Street, Suite 1400, Chicago, IL 60611-2951;  
Tel: 312-695-4036; Fax: 312-695-3999.

**Abstract:** Ambulatory pH monitoring is currently used to objectively demonstrate abnormal degrees of esophageal acid exposure in patients with suspected gastroesophageal reflux disease. The development of wireless pH capsule recording has improved the tolerability and increased the duration of pH recording. Use of symptom-reflux correlation measures and pH testing, combining periods off and on PPI therapy, serves to optimize the performance of conventional pH testing. On the other hand, devices that measure bile reflux as well as nonacid reflux (esophageal impedance testing) have broadened the definition of gastroesophageal reflux and present potential explanations for patients with continued symptoms despite high-dose PPI therapy. These advances and their current and future clinical applications are reviewed

Catheter-based, ambulatory pH monitoring is presently considered the best test for the diagnosis of gastroesophageal reflux disease (GERD), with greater sensitivity than endoscopy and greater specificity than an empiric trial of proton pump inhibitor (PPI) therapy. Recent technical advances in diagnostic systems such as the Bravo pH capsule monitoring system and esophageal impedance testing have improved our understanding and definitions of GERD. We provide a review of currently available ambulatory pH and reflux monitoring techniques and describe their unique advantages and limitations as well as their current role in the diagnosis of GERD.

## Bravo pH Monitoring: Technological Upgrade to a Tarnished Gold Standard

A significant advance in the diagnostic resources used to investigate GERD has been the advent of the Bravo pH capsule system (Medtronic, Minneapolis, Minn). This system uses a wireless, radio-telemetry pH capsule, which is affixed to the esophageal mucosa and transmits pH data to a small receiver worn by the patient. This system circumvents the need for the nasal placement of a traditional 24-hour pH catheter, thereby allowing for significant improvement in patient comfort. The Bravo pH capsule acquires data at 6-second intervals, differing from traditional catheter-based probes such as the

### Keywords

Gastroesophageal reflux disease, pH monitoring, impedance, Bilitec, chest pain, laryngitis

**Table 1.** Comparison Between Traditional Catheter Ambulatory pH Systems and the Bravo Wireless Capsule pH System

	Catheter	Bravo Wireless
Normative pH values (% time pH <4/24 hr in 95% controls)	<3.4–5.8%	<5.3%
Major advantages	Time tested cost	Patient tolerability Duration of recording Ability to combine off and on PPI periods in single study
Data sampling intervals	4–5 seconds	6 seconds
Study duration	24 hours	48–96 hours
Placement	Transnasal based on manometric landmark	Transnasal based on endoscopic landmark or based on manometric landmark
Patient discomfort	Nasal and pharyngeal irritation	Odynophagia and chest pain (usually mild)
Calibration	In vitro pre- and post-test	In vitro pre- and in vivo post-test
Other disadvantage	Potential for catheter displacement	Potential for premature capsule detachment

Slimline pH catheter system (0.25 Hz) (Medtronic, Minneapolis, MN) and the Sandhill pH catheter system (0.20 Hz) (Sandhill Scientific, Highlands Ranch, Col), which sample data at 4- and 5-second intervals, respectively. The wireless capsule allows data retrieval for a 48-hour study period, as compared to 24 hours with the standard catheter-based systems (see Table 1). In a study designed to evaluate the performance of the Bravo pH system in a group of healthy subjects, Pandolfino and colleagues<sup>1</sup> demonstrated that the abnormal threshold for percentage of time for distal esophageal acid exposure was 5.3%.

When comparing the Bravo capsule system to traditional catheter-based systems, several differences and advantages have been noted. During a study simultaneously comparing the Bravo capsule to the Slimline catheter pH system, a statistically significant difference was noted in the mean duration of acid exposure in normal

subjects (1.75% vs 3.5%, respectively).<sup>2,3</sup> This difference was attributed to a previously unnoticed error in a thermal calibration correction factor in the Slimline software that has since been corrected. The discrepancy may account for the elevated threshold pH values reported for the Bravo pH capsule compared with the Slimline catheter system.

Several studies have found the Bravo system to be better tolerated than catheter systems. Wong and associates<sup>4</sup> found that Bravo patients experienced less nose pain, throat pain, and headaches and were more likely to return to work during testing than patients using a catheter system (58% vs 11%). Patients who were evaluated with a catheter in this study spent more time sleeping or resting. In another comparison study, patients reported significantly higher satisfaction with the Bravo capsule based on symptoms and daily routine changes when compared to the catheter probe (0% vs 36%).<sup>1</sup> Both studies, however, reported a significantly higher proportion of patients with retrosternal chest discomfort with the Bravo system than with the catheter-based system. Capsule-associated chest discomfort may interfere with accurate symptom correlation with reflux episodes. Another study showed that activity during testing can affect the results of esophageal acid exposure. This study showed that exercise increases distal esophageal acid exposure in both GERD patients and normal controls.<sup>5</sup>

An important aspect of the standard catheter-based 24-hour ambulatory pH study is the accurate positioning of the pH probe. By convention, the probe is placed 5 cm above the proximal aspect of the lower esophageal sphincter (LES). It has been shown that pH probe migration can be initiated by swallowing, changing body position, food bolus size/type, and speech. Swallowing can alter the pH probe position by as much as 2 cm.<sup>6</sup> With respect to the LES, both more proximal and more distal placement can alter the sensitivity and specificity in diagnosing abnormal esophageal acid exposures.<sup>7,8</sup> Currently, the Bravo pH capsule is attached at 6 cm above the LES. This location has been shown to closely correlate with the location of the placement of the traditional catheter probe.<sup>2</sup> One study compared the placement of the Bravo capsule at both 1 and 6 cm above the squamocolumnar junction (SCJ).<sup>9</sup> As expected, the more distally placed capsule recorded a significantly higher amount of acid exposure. Although the more distal placement of the capsule increases the sensitivity for the diagnosis of acid reflux and, intuitively, the diagnosis of GERD, the clinical relevance of such an increase is not currently known and would likely compromise some degree of diagnostic test specificity.

#### **Limitations of the Bravo pH System**

The Bravo pH capsule system does have several distinct limitations and disadvantages. The capsule size makes transnasal passage problematic for many patients. There-

fore, the capsule is typically placed transorally using a landmark, the SCJ, which is ascertained by endoscopy. The Bravo capsule can also be positioned transorally using manometrically defined landmarks assuming that the manometric catheter is also placed transorally. If an endoscopy had been performed on an earlier date and the location of the SCJ were not recorded, a repeat endoscopy would be necessary, adding substantially to the procedure cost. Cost concerns are also important if a second Bravo capsule is needed because of primary attachment failure or premature capsule detachment. Additional cost would also be incurred if a second endoscopy is required in the unusual instance that a patient is unable to tolerate the capsule due to substernal pain or odynophagia. One early study reported recording periods of less than 48 hours in 30 out of 58 subjects. Of these 58 patients, 12% had primary attachment failure.<sup>10</sup> Subsequent modifications of the capsule have decreased early detachment rates and a recently published study reported obtaining pH data for at least 48 hours in greater than 90% of study patients.<sup>11</sup> An uncommon complication of the Bravo pH capsule system is the potential for esophageal perforation during placement of the catheter delivery system, which was reported in one case study.<sup>12</sup>

As previously mentioned, the Bravo system records data at a slower rate than catheter-based systems (every 6 seconds vs every 4–5 seconds). Measuring esophageal pH with more frequent sampling rates has been shown to detect an increase in the total number of reflux events.<sup>13</sup> However, such an increase in events was not shown to change overall total acid exposure. In one study, sampling frequency was found to contribute to less than 8% of the cumulative acidity measured. In addition, it was postulated that shorter-duration acid exposures are less clinically relevant than longer ones with lower pH nadirs, which would be detected with the Bravo pH system.<sup>3</sup> It should be noted that the Demeester score, a value calculated from the compilation of several pH-related parameters that include number of reflux events, may be affected by the Bravo system's slower data sampling. In addition, the Demeester score has not been validated with the Bravo pH system. The clinical relevance and effect on GERD symptom production from short-duration reflux events is currently unknown.

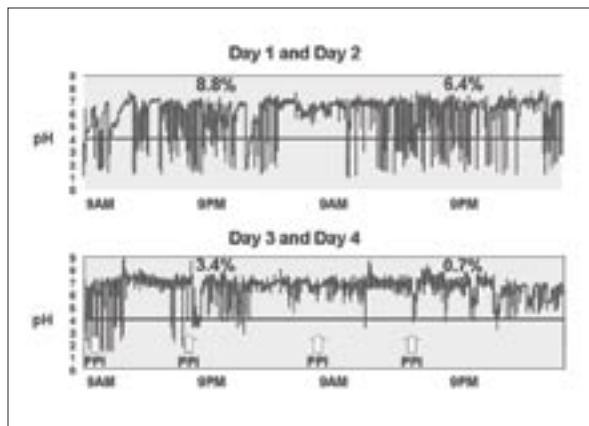
### Optimization of pH Studies: Extended Duration, Off- and On-PPI Testing, and Symptom Correlation Measures

In the evaluation of patients with suspected GERD, an extended duration of esophageal pH monitoring can be of significant value. Standard catheter study times range from 16 to 24 hours.<sup>14</sup> Wiener and colleagues<sup>15</sup> showed

that the results of 24-hour ambulatory pH catheter studies are reproducible with two studies performed in the same patient having an 89% intertest reproducibility. The Bravo ambulatory pH system can readily extend study times to at least 48 hours, with an early capsule detachment rate prior to 48 hours occurring only 10% of the time.<sup>1,16</sup> In contrast, the validity of using shorter test times has been studied as well. Arora and Murray compared a 3-hour postprandial test to a standard 24-hour ambulatory test and found that the shorter test had an 88% sensitivity and an 98% specificity.<sup>17</sup> However, it has been shown that using a 48-hour testing period significantly increases the diagnostic sensitivity and improves symptom correlation over a 24-hour recording, which can be of importance when evaluating both typical and atypical GERD symptoms.<sup>18</sup>

A common clinical question with regard to ambulatory esophageal pH monitoring is whether pH studies are optimally performed on or off PPI therapy. Off-therapy testing is most commonly used in two specific clinical scenarios. First, when there is a low index of suspicion that the patient's symptoms are related to GERD, the test is performed off therapy to rule out this diagnosis. Secondly, off-therapy testing is used to document the presence of abnormal acid exposure in patients without erosive esophagitis who are being considered for surgical or endoscopic therapy. When performed under such circumstances, however, an abnormal pH study needs to be interpreted with caution. The background prevalence of GERD is high, such that the demonstration of abnormal distal esophageal acid exposure alone does not imply causality for a patient's specific complaint. Furthermore, an abnormal test fails to evaluate the efficacy of medical therapy.

On-therapy testing, on the other hand, has its own set of advantages and disadvantages. PH monitoring while on PPI therapy is most commonly used in the evaluation of patients with persistent symptoms that are refractory to medical management. Although the likelihood of an abnormal pH test on PPI therapy is low, recent studies have demonstrated significant variability in the results of such testing. Charbel and coauthors<sup>19</sup> found that only 7% of patients with typical GERD symptoms had abnormal acid exposure times, and only 1% of patients with extra-esophageal symptoms had an abnormal test. At the other end of the spectrum, Milkes and colleagues<sup>20</sup> reported abnormal pH testing in 50% of a Veterans Administration patient population that had presented with typical reflux symptoms well-controlled with PPI therapy, the majority of whom were on twice-daily PPIs at the time of pH testing. In addition, it is unclear what should be considered normal acid exposure on PPI therapy. Using a 95% confidence interval, Kuo and Castell<sup>21</sup> showed



**Figure 1.** 96-hour Bravo pH recording combining periods both off and on proton pump inhibitor (PPI) therapy from a patient with significant gastroesophageal reflux. Initial esophageal exposure was 8.8% on day 1 and 6.4% on day 2, both off PPI therapy. Following the administration of omeprazole/sodium bicarbonate 40 mg PO bid, acid exposure decreased to 3.4% on day 3, 0.7% on day 4.

that normal acid exposure time of pH less than 4 was less than 1.6% in healthy adults treated with 40 mg of omeprazole daily. This value is more stringent than the traditional 4–5% threshold values that are based on pH monitoring studies in healthy individuals off PPI therapy. Without further evidence to suggest added clinical utility in using the more rigorous pH threshold for patients on PPI therapy, the traditional normal references are generally employed.

A recent study evaluated the feasibility of a 4-day Bravo capsule study that allows for combined pH testing off and on PPI therapy in the same study. Patients were placed on twice-daily rabeprazole on day 2 of the study. Capsule detachment occurred prior to day 4 in 5% of patients. By day 4 of the study, 95% of patients had normalization of acid exposure times. The 4-day Bravo protocol combines the benefits of both on and off PPI therapy in one study. Furthermore, looking at symptoms in the presence and absence of abnormal acid exposure adds confidence in the assessment of symptom-reflux correlation. The technique adds the dimension of a “dose-response” assessment of acid exposure versus typical or atypical reflux symptoms. Extending the off-therapy phase of the recording protocol to 48 from 24 hours would increase the sensitivity of abnormal reflux detection with the potential downside of increasing the number of studies with incomplete on-therapy testing due to early capsule detachment. Figure 1 depicts a 4-day Bravo study performed with the first 48 hours off PPI therapy and the second 48 hours on omeprazole/sodium bicarbonate 40 mg twice daily, illustrating normalization of distal acid exposure with therapy.

Several indices have been developed to optimize the interpretation of pH testing by statistically correlating individual reflux events with symptoms. Some of these indices have had significant limitations in overestimating a causal relationship due to inherent errors such as chance associations or an infrequent number of symptomatic reflux events. The most intuitive method is the symptom index (SI), which is simply the percentage of symptoms associated with reflux divided by the total number of symptoms. A related measure is the symptom sensitivity index (SSI). The SSI is insensitive to the number of patient symptoms, which may affect its accuracy. The most statistically robust symptom-reflux correlation scheme is the symptom-association probability (SAP) analysis.<sup>22</sup> The SAP uses a contingency table of positive and negative reflux events coupled with symptoms to determine the statistical validity between these factors, thereby limiting chance associations. It should be noted that none of the available symptom correlation measures have been well validated in the clinical setting, especially with regard to outcome studies of medical or surgical intervention. One study found that such measures have limited ability to predict the response to high-dose PPI therapy.<sup>23</sup> Therefore, at this time, an abnormal symptom association measure by itself should be viewed as complementary information in the evaluation of GERD and should not be the basis for major therapeutic recommendations such as fundoplication.

### Intragastric pH Recording: Is There Clinical Utility?

Some interest has been generated in the evaluation of intragastric acidity and its effect on GERD with the use of an intragastric pH probe. The probe is identical to a standard esophageal probe but is placed 10 cm below the LES, situating it in the gastric fundus or body. Some association between esophageal mucosal healing and gastric pH levels has been demonstrated.<sup>24</sup> As would be expected, control of gastric pH on PPI therapy is substantially less than that in the esophagus. Since PPIs are all highly effective in normalizing esophageal acid exposure, gastric pH control has been used as an intermediate marker of PPI potency. One study showed intragastric pH to be greater than 4 only 70% of the time on twice-daily PPI therapy.<sup>25</sup> Intragastric acid exposure is greatest at night—leading to the development of the term nocturnal acid breakthrough (NAB). NAB is defined as a pH less than 4 for more than 1 hour while on PPI therapy. Although these data seem significant, several studies have shown a poor correlation between NAB and distal esophageal acid exposure or GERD symptoms.<sup>26–29</sup> The clinical use of intragastric pH monitoring has been limited due to test limitations such as inability to distinguish the volume of gastric acid

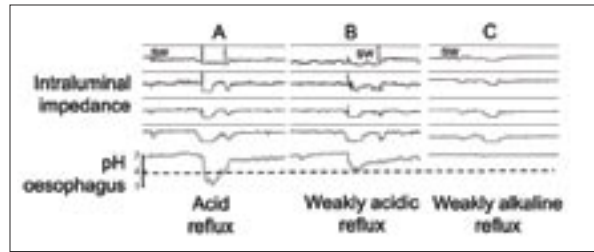
exposure in the stomach, inability to account for food or duodenal alkaline reflux, and significant intertest result variability.<sup>27,30</sup> Although not recommended for routine clinical practice, gastric pH recordings have been increasingly used as a more rigorous but intermediary endpoint for evaluating the efficacy of novel acid-suppressing agents.

### Bilitec Testing: A Possible Role for Bile Reflux?

Paralleling the interest in gastric acidity and its effect on GERD symptoms has been investigation into the importance of duodenogastroesophageal reflux (DGER). DGER consists of the reflux of duodenal contents such as biliary and pancreatic secretions and bicarbonate into the esophageal lumen. In 1993, Bechi and colleagues<sup>31</sup> developed a new technique for the ambulatory detection of enterogastric and nonacidic reflux using a fiber optic sensor that utilizes the optical properties of bile, serving as the basis for the commercially available Bilitec system (Medtronic, Minneapolis, Minn). However, over a decade later, the clinical relevance of DGER and its association with symptoms and esophageal mucosal damage remain controversial. Vaezi and colleagues<sup>32</sup> showed that a majority of DGER events occur in the setting of significant esophageal acid exposure (pH <4). They also demonstrated that acid and DGER show a graded increase in severity across the GERD spectrum and both occur simultaneously in reflux episodes. Data from one study suggested that symptoms of GERD are more related to acid reflux than bile reflux and the latter did not seem to play a major role in symptom production. In addition, the use of PPI therapy was shown to simultaneously decrease both acid reflux and DGER.<sup>33-35</sup> These data call into question the clinical utility of DGER testing. Recently, however, Tack and associates<sup>36</sup> showed that there may be clinical significance in detecting reflux using DGER testing in a subpopulation of symptomatic patients who were refractory to PPI therapy. There is also evidence that using a GABA-B agonist such as baclofen may be useful in decreasing DGER by modifying transient LES relaxations and therefore decreasing symptoms.<sup>37</sup> The Bilitec system has been utilized in clinical studies by only a few centers and has very limited commercial availability. Additional studies are needed before its use in clinical practice can be recommended.

### Esophageal Impedance Testing: What Is the Clinical Significance of Nonacid Reflux?

A major technological advance in reflux testing is the incorporation of impedance testing. Impedance detects



**Figure 2.** Definitions of reflux based on changes in impedance are further characterized based on the pH of the refluxate. Acid reflux (A) is defined as reflux that reduces esophageal pH below 4. Weakly acidic reflux (B) is defined as a pH fall of at least 1 unit where the pH falls below 7 but is above 4. Weakly alkaline reflux (C) is defined as a reflux episode detected on impedance during which nadir esophageal pH does not drop below 7.<sup>41</sup>

Sifrim D, et al. *Gut*. 2004;53:1024-1031.

changes in resistance to current flow when a bolus of air, liquid, or food traverses a series of paired electrodes. These electrodes can detect substance distribution, composition, and clearance times. With the incorporation of impedance into the traditional catheter pH probes, additional descriptive reflux categories have been termed: acid, weakly acid, and weakly alkaline reflux (Figure 2).<sup>38</sup> The differentiation of these categories has allowed for the more accurate evaluation of both acid and nonacid reflux. Impedance testing has been validated against traditional pH testing with one study showing approximately 95% of acid reflux events being detected with impedance testing.<sup>39</sup> Direct comparisons between GERD patients and normal controls using impedance have been performed. These show a similar frequency of overall reflux episodes between the two groups but a significantly higher number of acid reflux events in GERD patients.<sup>40</sup> During treatment with omeprazole, one group showed that reflux becomes predominately nonacid in composition.<sup>41</sup> Although symptoms in this group were most commonly associated with acid reflux, some symptomatic episodes were reported with nonacidic reflux as well. This demonstrates a potential role for impedance testing in the clinical evaluation of patients who fail to respond to PPI therapy. Shay<sup>42</sup> suggested that this test may be best used to study patients on PPI therapy in order to answer three specific questions with one study: (1) Is acid suppression adequate? (2) Does nonacid reflux play a role in the patient's symptoms? (3) What is the reflux frequency? A recently published study showed that the addition of impedance to esophageal pH monitoring in patients not on PPI therapy led to an increase in correlation of reflux episodes and symptoms.<sup>43</sup> Current limitations of impedance testing include lengthy study interpretation time and

an evaluator learning curve. Distinguishing entities that can mimic reflux events such as swallows and baseline tracing variations can be difficult. Furthermore, the clinical interpretation of impedance studies relies upon use of a symptom correlation analysis such as the SI, SSI, or SAP. The therapeutic implications of an abnormal symptom association in a patient on PPI therapy with normal distal esophageal acid exposure is, as yet, unproven by current studies. Additional studies examining the clinical utility of impedance testing in patients with GERD are needed.

## Clinical Applications of Reflux Testing

### *Management of Patients With Typical Reflux With or Without Complications*

In the clinical application of ambulatory reflux studies, reflux testing on patients who have significant symptom relief on pharmacologic therapy is generally not indicated. One exception to this is a patient with nonerosive reflux disease being considered for endoscopic or surgical treatment of GERD, where testing is often performed off PPI therapy. PH testing is also not recommended in patients with obvious reflux-related manifestations such as erosive esophagitis, Barrett esophagus, or peptic stricture. Multiple studies have shown that greater degrees of distal esophageal acid exposure are correlated with increased lengths of Barrett esophagus.<sup>44,45</sup> Barrett patients have been shown to have a higher likelihood of abnormal distal esophageal acid exposure despite use of PPI therapy and resolution of symptoms on medical therapy.<sup>46</sup> One study demonstrated that up to 24% of Barrett patients on high-dose twice-daily omeprazole therapy had abnormal acid exposure in the distal esophagus.<sup>47</sup> Therefore patients who have Barrett esophagus may benefit from pH testing to document adequate acid suppression although the clinical utility of this is unproven. Future studies are needed to delineate whether improved acid suppression equates with a clinically significant reduction in risk of progression of complicated GERD.

A common clinical scenario is the patient with continued heartburn symptoms despite what is deemed adequate medical or surgical reflux management. Several studies have found 90% or greater normalization of esophageal acid exposure on medical treatment.<sup>27,48,49</sup> These data suggest that studying these patients with esophageal pH testing is unlikely to be useful. However, when using a previously delineated, more stringent cut-off for normal distal esophageal acid exposure (pH <4, >1.6% of time), Katzka and colleagues found that 56% of patients with refractory heartburn had abnormal acid exposure.<sup>50</sup> Alternately, a normal pH study in patients with heartburn that is refractory to PPI therapy argues against increased acid suppressant therapy or surgical

fundoplication. The addition of a symptom-reflux analytic scheme such as the SAP may be of added benefit in excluding possible acid hypersensitivity. Although a negative pH study and symptom association may rule out acid reflux, nonacidic reflux is not excluded as the source of ongoing symptoms. The clinical significance of nonacid reflux, however, remains uncertain. Impedance or Bilitest testing may have a significant role in the evaluation of such patients in the near future.

### *Management of Patients With Extraesophageal Manifestations of GERD*

It has been shown that as many as 60% of patients with noncardiac chest pain have abnormal pH studies.<sup>51</sup> An initial therapeutic trial of PPI therapy is recommended in such patients although one must accept a significant false-positive response rate owing to placebo effect.<sup>52-54</sup> If a PPI trial fails, pH testing can be helpful in supporting or refuting GERD as an etiology. A normal pH study off PPI therapy combined with a negative symptom correlation measure provides strong evidence against GERD as the etiology of the chest pain.

GERD has also been associated with several extraesophageal manifestations, including hoarseness, chronic cough, chronic laryngeal symptoms, and asthma. A causal link between pharyngeal acid exposure and such symptoms and clinical findings has not been established.<sup>55,56</sup> Studies have shown poor correlation between either proximal or distal esophageal exposure and chronic laryngeal symptoms and signs. Moreover, several recent randomized controlled trials have not demonstrated significant improvement in laryngeal symptoms or signs with twice-daily PPI therapy compared with placebo. One study did report that proximal esophageal acid exposure of greater than 1.1% was predictive of asthma that improved with PPI therapy. However, the utility of reflux testing in asthmatic patients remains controversial and empiric therapeutic trials of PPI therapy are recommended prior to consideration of pH monitoring.<sup>57</sup>

## Future Technologies

As noted, ongoing studies are investigating the importance of nonacid, weakly acid, and bile acid esophageal reflux to define roles for the emerging technologies of impedance and bile acid monitoring. In some patients, chest pain and heartburn may have causes other than reflux disease such as esophageal dysmotility. Studies are examining the value of prolonged ambulatory monitoring of esophageal motility using not only manometry but also high-frequency ultrasound devices. At the same time, miniaturization and wireless technological advances continue. Wireless monitoring of gastric and small intestinal pH and motility is

already being examined. In addition, current technologies are being combined to form multimodal devices to better differentiate the pathophysiology of GERD and esophageal disorders that evoke similar symptom presentations.<sup>58</sup> As such technology advances, it needs to be recognized that the majority of patients referred to gastroenterologists have symptoms that remain poorly defined by any objective testing parameter and continue to fall in the realm of functional gastrointestinal disorders.

## References

- Pandolfino JE, Richter JE, Ours T, et al. Ambulatory esophageal pH monitoring using a wireless system. *Am J Gastroenterol*. 2003;98:740-749.
- Pandolfino JE, Schreiner MA, Lee TJ, et al. Comparison of the Bravo wireless and Digitrapper catheter-based pH monitoring systems for measuring esophageal acid exposure. *Am J Gastroenterol*. 2005;100:1466-1476.
- Pandolfino JE, Schreiner MA, Ghosh S, et al. Acid reflux event detection using the Bravo wireless versus the Slimline catheter pH systems: why are the numbers so different? *Gut*. 2005;54:1687-1692.
- Wong WM, Bautista J, Dekel R, et al. Feasibility and tolerability of transnasal/per-oral placement of the wireless pH capsule vs. traditional 24-h esophageal pH monitoring—a randomized trial. *Aliment Pharmacol Ther*. 2005;21:155-163.
- Pandolfino JE, Bianchi LK, Lee TJ, et al. Esophagogastric junction morphology predicts susceptibility to exercise-induced reflux. *Am J Gastroenterol*. 2004;99:1430-1436.
- Aksglaede K, Funch-Jensen P, Thommesen P. Intra-esophageal pH probe movement during eating and talking. A videoradiographic study. *Acta Radiol*. 2003;44:131-135.
- Anggiansah A, Sumboonnanonda K, Wang J, et al. Significantly reduced acid detection at 10 centimeters compared to 5 centimeters above lower esophageal sphincter in patients with acid reflux. *Am J Gastroenterol*. 1993;88:842-846.
- Fletcher J, Wirz A, Henry E, McColl KE. Studies of acid exposure immediately above the gastro-oesophageal squamocolumnar junction: evidence of short segment reflux. *Gut*. 2004;53:168-173.
- Pandolfino J, Schreiner M, Zhang Q, et al. Comparison of esophageal acid exposure at 1 cm and 6 cm above the squamocolumnar junction using the Bravo pH monitoring system. *Dis Esophagus*. 2006;19:177-182.
- Ward EM, DeVault KR, Bouras EP, et al. Successful oesophageal pH monitoring with a catheter-free system. *Aliment Pharmacol Ther*. 2004;19:449-454.
- Ahlawat SK, Novak DJ, Williams DC, Maher KA, et al. Day-to-day variability in acid reflux patterns using the BRAVO pH monitoring system. *J Clin Gastroenterol*. 2006;40:20-24.
- Fajardo NR, Wise JC, Locke GR, et al. Esophageal perforation after placement of wireless Bravo pH probe. *Gastrointest Endosc*. 2005;63:84-85.
- Emde C, Garner A, Blum AL. Technical aspects of intraluminal pH-metry in man: current status and recommendations. *Gut*. 1987;28:1177-1188.
- Ergun GA, Kahrilas PJ. Clinical applications of esophageal manometry and pH monitoring. *Am J Gastroenterol*. 1996;91:1077-1089.
- Wiener GJ, Morgan TM, Copper JB, et al. Ambulatory 24-hour esophageal pH monitoring. Reproducibility and variability of pH parameters. *Dig Dis Sci*. 1988;33:1127-1133.
- Hirano I, Zhang Q, Pandolfino JE, Kahrilas PJ. Four-day Bravo pH capsule monitoring with and without proton pump inhibitor therapy. *Clin Gastroenterol Hepatol*. 2005;3:1083-1088.
- Arora AS, Murray JA. Streamlining 24-hour pH study for GERD: Use of a 3-hour postprandial test. *Dig Dis Sci*. 2003;48:10-15.
- Prakash C, Clouse RE. Value of extended recording time with wireless pH monitoring in evaluating gastroesophageal reflux disease. *Clin Gastroenterol Hepatol*. 2005;3:329-334.
- Charbel S, Khandwala F, Vaezi MF. The role of esophageal pH monitoring in symptomatic patients on PPI therapy. *Am J Gastroenterol*. 2005;100: 283-289.
- Milkes D, Gerson LB, Triadafilopoulos G. Complete elimination of reflux symptoms does not guarantee normalization of intrasophageal and intragastric pH in patients with gastroesophageal reflux disease (GERD). *Am J Gastroenterol*. 2004;99:991-996.
- Kuo B, Castell DO. Optimal dosing of omeprazole 40 mg daily: effects on gastric and esophageal pH and serum gastrin in healthy controls. *Am J Gastroenterol*. 1996;91:1532-1538.
- Weusten BL, Roelofs JM, Akkermans LM, et al. The symptom-association probability: an improved method for symptom analysis of 24-hour esophageal pH data. *Gastroenterology*. 1994;107:1741-1745.
- Taghavi SA, Ghasedi M, Saberi-Firoozi M, et al. Symptom association probability and symptom sensitivity index: preferable but still suboptimal predictors of response to high dose omeprazole. *Gut*. 2005;54:1067-1071.
- Bell NJ, Burget D, Howden CW, et al. Appropriate acid suppression for the management of gastro-oesophageal reflux disease. *Digestion*. 1992;51(Suppl 1):59-67.
- Katz, PO, Anderson C, Khoury R, Castell DO. Gastro-oesophageal reflux associated with nocturnal gastric acid breakthrough on proton pump inhibitors. *Aliment Pharmacol Ther*. 1998;12:1231-1234.
- Fackler WK, Ours TM, Vaezi MF, Richter JE. Long-term effect of H2RA therapy on nocturnal gastric acid breakthrough. *Gastroenterology*. 2002;122:625-632.
- Ours TM, Fackler WK, Richter JE, Vaezi MF. Nocturnal acid breakthrough: clinical significance and correlation with esophageal acid exposure. *Am J Gastroenterol*. 2003;98:545-550.
- Hicks DM, Ours TM, Abelson TI, et al. The prevalence of hypopharynx findings associated with gastroesophageal reflux in normal volunteers. *J Voice*. 2002;16:564-579.
- Orr WC, Harnish MJ. The efficacy of omeprazole twice daily with supplemental H2 blockade at bedtime in the suppression of nocturnal oesophageal and gastric acidity. *Aliment Pharmacol Ther*. 2003;17:1553-1558.
- Katz PO, Hatlebakk JG, Castell DO. Gastric acidity and acid breakthrough with twice-daily omeprazole or lansoprazole. *Aliment Pharmacol Ther*. 2000;14:709-714.
- Bechi P, Pucciani F, Baldini F, et al. Long-term ambulatory enterogastric reflux monitoring. Validation of a new fiberoptic technique. *Dig Dis Sci*. 1993;38:1297-1306.
- 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.
- Champion G, Richter JE, Vaezi MF, et al. Duodenogastric reflux: relationship to pH and importance in Barrett's esophagus. *Gastroenterology*. 1994;107:747-754.
- Marshall RE, Anggiansah A, Manifold DK, et al. Effect of omeprazole 20 mg twice daily on duodenogastric and gastro-oesophageal bile reflux in Barrett's esophagus. *Gut*. 1998;43:603-606.
- Netzer P, Gut A, Brundler R, et al. Influence of pantoprazole on oesophageal motility, and bile and acid reflux in patients with oesophagitis. *Aliment Pharmacol Ther*. 2001;15:1375-1384.
- Tack J, Koek G, Demedts I, et al. Gastroesophageal reflux disease poorly responsive to single-dose proton pump inhibitors in patients without Barrett's esophagus: acid reflux, bile reflux, or both? *Am J Gastroenterol*. 2004;99:981-988.
- Koek GH, Sifrim D, Lerut T, et al. Effect of the GABA(B) agonist baclofen in patients with symptoms and duodeno-gastro-oesophageal reflux refractory to proton pump inhibitors. *Gut*. 2003;52:1397-1402.
- Sifrim D, Castell D, Dent J, Kahrilas PJ. Gastro-oesophageal reflux monitoring: review and consensus report on detection and definitions of acid, non-acid, and gas reflux. *Gut*. 2004;53:1024-1031.
- Shay SS, Bomeli S, Richter J. Multichannel intraluminal impedance accurately detects fasting, recumbent reflux events and their clearing. *Am J Physiol Gastrointest Liver Physiol*. 2002;283:G376-G383.
- Zerbib F, Roman S, Pouderooux P, et al. 24 hour ambulatory esophageal multichannel intraluminal impedance-pH in healthy European subjects. *Gastroenterology*. 2005;128:A-396.
- Vela MF, Camacho-Lobato L, Srinivasan R, et al. Simultaneous intraesophageal impedance and pH measurement of acid and nonacid gastroesophageal reflux: effect of omeprazole. *Gastroenterology*. 2001;120:1599-1606.
- Shay S. Esophageal impedance monitoring: the ups and downs of a new test. *Am J Gastroenterol*. 2004;99:1020-1022.
- Bredenoord AJ, Weusten BL, Timmer R, et al. Addition of esophageal impedance monitoring to pH monitoring increases the yield of symptom association analysis in patients off PPI therapy. *Am J Gastroenterol*. 2006;101:453-459.
- Oberg S, DeMeester TR, Peters JH, et al. The extent of Barrett's esophagus depends on the status of the lower esophageal sphincter and the degree of esophageal acid exposure. *J Thorac Cardiovasc Surg*. 1999;117:572-580.
- Fass R, Hell RW, Garewal HS, et al. Correlation of oesophageal acid exposure

- with Barrett's oesophagus length. *Gut*. 2001;48:310-313.
46. Katzka DA, Castell DO. Successful elimination of reflux symptoms does not insure adequate control of acid reflux in patients with Barrett's esophagus. *Am J Gastroenterol*. 1994;89:989-991.
47. Fass R. Empirical trials in treatment of gastroesophageal reflux disease. *Dig Dis*. 2000;18:20-26.
48. Robinson M, Maton PN, Allen ML, et al. Effect of different doses of omeprazole on 24-hour oesophageal acid exposure in patients with gastro-oesophageal reflux. *Aliment Pharmacol Ther*. 1991;5:645-651.
49. Robinson M, Maton PN, Rodriguez S, et al. Effects of oral rabeprazole on oesophageal and gastric pH in patients with gastro-oesophageal reflux disease. *Aliment Pharmacol Ther*. 1997;11:973-980.
50. Katzka DA, Paoletti V, Leite L, Castell DO. Prolonged ambulatory pH monitoring in patients with persistent gastroesophageal reflux disease symptoms: testing while on therapy identifies the need for more aggressive anti-reflux therapy. *Am J Gastroenterol*. 1996;91:2110-2113.
51. Tack J. The Esophagus and non-cardiac chest pain. In: Castell DO, Richter JE, eds. *The Esophagus*, 4th ed. 2004. Philadelphia. Lippincott, Williams & Wilkins. p. 634-647.
52. Cremonini F, Wise J, Moayyedi P, Talley NJ. Diagnostic and therapeutic use of proton pump inhibitors in non-cardiac chest pain: a metaanalysis. *Am J Gastroenterol*. 2005;100:1226-1232.
53. Fass R, Fennerty MB, Ofman JJ, et al. The clinical and economic value of a short course of omeprazole in patients with noncardiac chest pain. *Gastroenterology*. 1998;115:42-49.
54. Ofman JJ, Gralnek IM, Udani J, et al. The cost-effectiveness of the omeprazole test in patients with noncardiac chest pain. *Am J Med*. 1999;107:219-227.
55. Shaker R, Milbrath M, Ren J, et al. Esophagopharyngeal distribution of refluxed gastric acid in patients with reflux laryngitis. *Gastroenterology*. 1995;109:1575-1582.
56. Ulualp SO, Toohill RJ, Shaker R. Outcomes of acid suppressive therapy in patients with posterior laryngitis. *Otolaryngol Head Neck Surg*. 2001;124:16-22.
57. Sifrim D, Dupont L, Blondeau K, et al. Weakly acidic reflux in patients with chronic unexplained cough during 24 hour pressure, pH, and impedance monitoring. *Gut*. 2005;54:449-454.
58. Bredenoord AJ, Weusten BL, Timmer R, Smout AJ. Intermittent spatial separation of diaphragm and lower esophageal sphincter favors acidic and weakly acidic reflux. *Gastroenterology*. 2006;130:334-340.