

# Ambulatory Esophageal pH Monitoring Using a Wireless System

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**OBJECTIVES:** Limitations of catheter-based esophageal pH monitoring are discomfort, inconvenience, and interference with normal activity. An alternative to conventional pH monitoring is the wireless Medtronic Bravo pH System. The aim of this study was to evaluate the safety, performance, and tolerability of this system.

**METHODS:** A total of 44 healthy subjects and 41 patients with gastroesophageal reflux disease (GERD) were studied for a 2-day period. The pH telemetry capsule was positioned transorally 6 cm above the squamocolumnar junction using endoscopic measurement. The signal transmitted from the capsule was received and recorded by a small, pager-sized receiver, and pH data were subsequently uploaded to a computer for analysis.

**RESULTS:** Successful 24-h pH studies were completed in 82 subjects (96%). During the 24-h study period the median percentage of the time that pH was <4 was 2.3% (95th percentile, 5.9%) in controls and 6.5% (range, 0.8–27.6) in GERD patients. In 76 subjects (89%), 36–48 h recordings were obtained. For the extended period the median percentage of the time that pH was <4 was 2.0% (95th percentile, 5.3%) in controls and 6.6% (range, 1.0–26.7) in GERD patients. Capsules required endoscopic removal in three subjects (4%). Optimal sensitivity in distinguishing controls from reflux patients was achieved when analyzed from the perspective of the worst of the 2 days.

**CONCLUSION:** The wireless Bravo pH System successfully recorded esophageal acid exposure in 96% of the patients during a 24-h period and in 89% of subjects for >36 h. The 95th percentile for the 2-day recordings in control subjects was 5.3%, slightly higher than observed with conventional systems. (*Am J Gastroenterol* 2003;98:740–749. © 2003 by Am. Coll. of Gastroenterology)

## INTRODUCTION

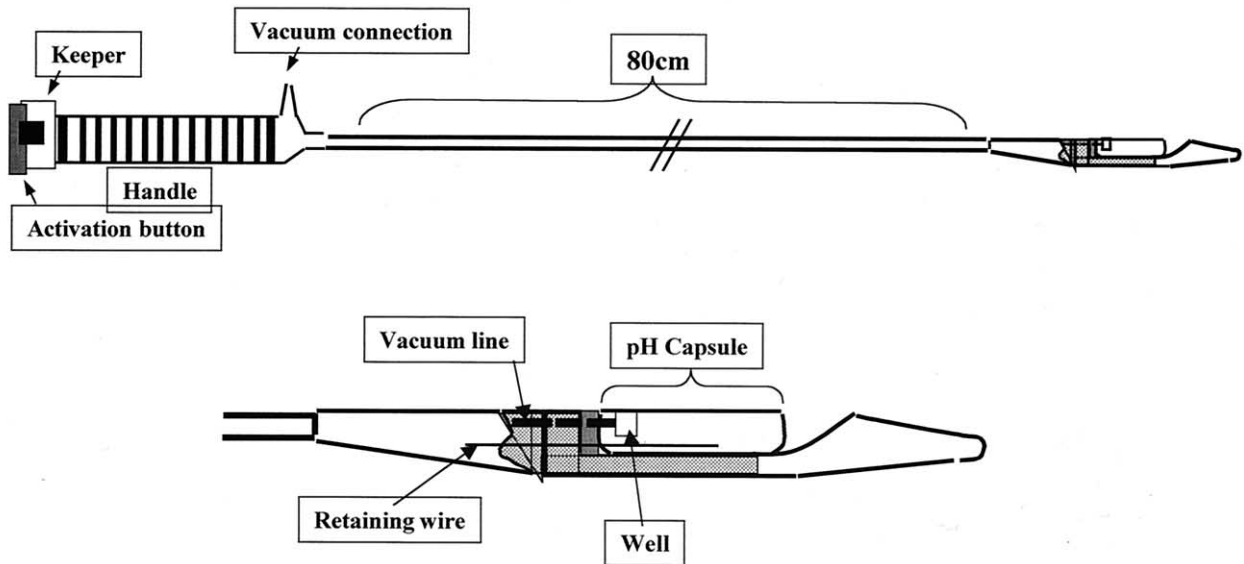
Extended esophageal pH monitoring can be of considerable value in managing patients with typical or atypical symptoms who seem refractory to standard therapy for gastroesophageal reflux disease (GERD) (1). Current ambulatory esophageal pH recording methodology entails passing a pH

electrode transnasally into the esophagus and positioning it 5 cm above the manometrically defined upper border of the lower esophageal sphincter (LES). Wires from the electrode are housed in a catheter that exits from the nose and is plugged into a data-logger that is either strapped to the patient or attached to their belt. Gastroesophageal reflux can be quantified and specific patterns of reflux can be evaluated using this technique for periods of 16 to 24 h. This is currently the standard technique for quantifying esophageal acid exposure.

Despite being the most reliable technique for quantifying acid exposure in the esophagus, ambulatory pH monitoring has significant methodological limitations. The nasally passed pH electrode is uncomfortable and conspicuous leading most patients to modify their daily activities and/or diet (2). In some instances, patients simply remain at home, engaging in minimal physical activity and eating scantily because of the discomfort associated with swallowing. The resultant study may be viewed as a false-negative if the obligatory dietary and activity limitations reduce esophageal acid exposure to within “normal” limits. In addition, placement of the pH electrode is a crucial methodological detail in pH studies with the current standard practice requiring esophageal manometry to first localize the position of the LES relative to the nares (1). Either proximal and distal electrode placement can potentially alter the diagnosis in a significant proportion of patients (3, 4). Thus, the methodology of esophageal pH monitoring could be substantially improved and simplified with a more comfortable recording apparatus and a simpler means of determining and maintaining proper electrode location.

The Medtronic (Shoreview, MN) Bravo pH monitoring system is a new United States Food and Drug Administration class I approved, “catheterless” pH monitoring system. This pH system involves the attachment of a radiotelemetry pH capsule to the mucosal wall of the esophagus. It simultaneously measures pH and transmits data to a pager-sized receiver clipped onto the patient’s belt, thereby circumventing the need for a nasally placed catheter and fixing the electrode to a defined position on the esophageal mucosa. A pilot study evaluating simultaneous catheter-based pH monitoring and Bravo pH monitoring revealed that the two

## Bravo capsule and delivery system



**Figure 1.** Prepackaged assembly incorporating both a delivery system and the capsule itself. The handle of the delivery system is separated from the end housing the capsule by a tubular component (length 80 cm, diameter 6F). The plastic keeper is removed before pressing the activation plunger and pin firing.

techniques were comparable in quantifying esophageal acid exposure (5). The primary aims of this study were to evaluate the safety, performance, and tolerability of this wireless pH recording system.

### MATERIALS AND METHODS

#### Subjects

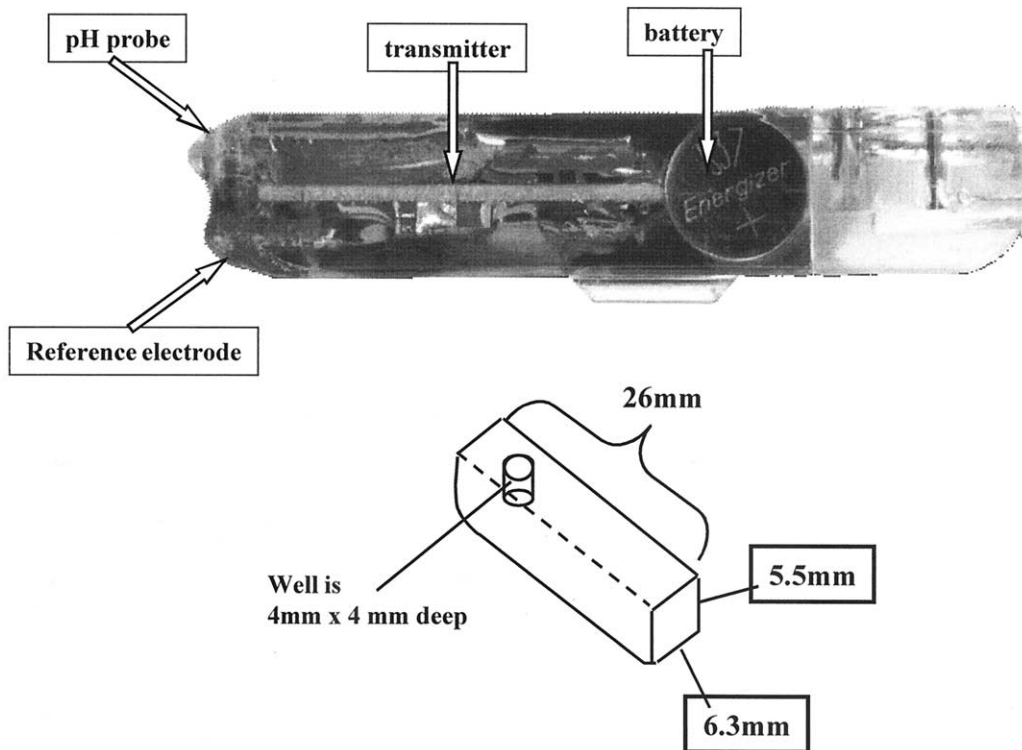
A total of 44 healthy controls (13 men and 31 women, 23–53 yr old) with no history of heartburn, reflux, chest pain, or atypical symptoms, as well as 41 patients with GERD (26 men and 15 women, 32–72 yr old) were studied. The controls and GERD patients were enrolled from the GI Diagnostic Laboratories at Northwestern Memorial Hospital and at the Cleveland Clinic Foundation Hospital. Four GERD subjects were referred after refusing standard catheter-based pH monitoring, and another eight GERD subjects were referred after failing to tolerate a pH study using a transnasally placed catheter. The protocol for this study was approved by the Northwestern University and The Cleveland Clinic Foundation Institutional Review Boards, and informed consent was obtained from all participants.

None of the subjects had a history of surgical manipulation of the upper GI tract. Other exclusion criteria included a history of bleeding diathesis or coagulopathy, stroke or transient ischemic attack within the past 6 months, significant medical illness (*i.e.*, congestive heart failure), significant GI bleed within the past 6 months, and esophageal varices. Normal controls had no abdominal symptoms, no use of antacids or antisecretory medication, and normal endoscopy. Of the 41 GERD patients, 25 subjects had ero-

sive esophagitis and 16 had normal endoscopy. Of the endoscopy negative GERD subjects, six had an abnormal 24 h pH study before the Bravo study. Additionally, 10 endoscopy negative GERD patients were diagnosed clinically with typical GERD symptoms of heartburn and regurgitation that resolved with proton pump inhibitor therapy. GERD patients stopped taking proton pump inhibitors 7 days before the study, histamine-2 receptor antagonists 5 days before the study, and antacids 24 h before the study.

#### Bravo pH Capsule and Monitoring System

The pH capsule was attached to the esophageal mucosa using a prepackaged assembly, which incorporated both a delivery system and the capsule itself (Fig. 1). The handle of the delivery system is separated from the end housing the capsule by a tubular component (80 cm length, 6F diameter). The delivery system was designed for either oral or nasal passage. The actual pH capsule is oblong in shape ( $6 \times 5.5 \times 25$  mm). A well (4-mm diameter  $\times$  3.5-mm deep) is located on the superior-lateral aspect of the probe. The well is connected to a custom made vacuum unit capable of generating 600 mm Hg vacuum pressure to the well via the delivery system. An antimony pH electrode and reference electrode are located on the distal tip of the capsule, and an internal battery and transmitter are contained within the capsule (Fig. 2). The electronics and sensor are all encapsulated in epoxy. The pH capsule sends a data signal to the external receiver via radiofrequency telemetry. The carrier frequency for the pH signal is in the unregulated 433-MHz band. Data security is accomplished by digital data trans-



**Figure 2.** The dimensions and electronics of the capsule. The capsule is oblong ( $6 \times 5.5 \times 25$  mm). A well (diameter 4 mm, depth 3.5 mm) is located on the superior-lateral aspect of the probe. The well is connected to a custom made vacuum unit capable of generating 600 mm Hg vacuum pressure to the well via the delivery system. An antimony pH electrode and reference electrode are located on the distal tip of the capsule, and an internal battery and transmitter are contained within the capsule.

mission and by encoding each capsule with a unique identification code that is transmitted every 12 s, along with two pH data points obtained at 6-s sampling intervals. Before placement, the capsule is activated by a magnetic switch and calibrated by submersion in pH buffer solutions of pH 7.0 and pH 1.68 (Exalol, Clearwater, FL). In the process, the capsule and receiver are also checked to confirm proper functioning of data transmission and receiving hardware.

#### **Placement of the pH Capsule**

All subjects underwent an overnight fast before arrival at the endoscopy laboratory. Subjects underwent upper endoscopy in the left lateral decubitus position to measure the distance between the squamocolumnar junction and incisors, as well as to evaluate for esophagitis and hiatus hernia. Conscious sedation with 1–5 mg midazolam and 50–75 mg meperidine was used if requested by the subjects. After completion of upper endoscopy, the endoscope was removed and the delivery system passed orally into the esophagus. Using endoscopic measurement of the squamocolumnar junction, the pH probe was positioned such that the pH electrode at the distal end was 6 cm above the squamocolumnar junction. The 6-cm distance was derived from a previously published analysis of the relative locations of the LES high pressure zone and the squamocolumnar junction (6). That study concluded that the proximal extent of the LES high pressure zone was typically 1–1.5 cm proximal to the squamocolum-

nar junction; therefore, placement of the pH electrode 6 cm above the squamocolumnar junction approximated the conventional placement method targeting a position 5 cm proximal to the upper margin of the LES. Patients with circumferential Barrett's metaplasia would require an alternative placement method.

The delivery system was introduced orally with the patient remaining in the same left lateral decubitus position assumed during endoscopy. With the delivery system placed in the esophagus and positioned so that the pH electrode was 6 cm above the Squamocolumnar junction (SCJ), the external vacuum pump was switched on to apply suction to the well of the pH capsule, sucking in the adjacent esophageal mucosa. Successful capture of esophageal mucosa was assumed when the vacuum gauge on the pump stabilized at a value  $>510$  mm Hg for 10 s. The plastic safety guard on the handle was then removed and the activation button depressed. This activated a spring-loaded, stainless steel pin to be driven through the well of the pH capsule, tangential to the axis of the esophagus, securing the esophageal mucosa within the well and, in the process, attaching the pH capsule to the esophageal wall. The activation button on the handle was then twisted clockwise  $90^\circ$  and re-extended, which had the effect of releasing the pH capsule from its attachment point on the delivery system. The delivery system was then removed. In some cases, esophagoscopy was repeated to

document capsule attachment, with care taken not to dislodge it. With the capsule attached, pH recording was initiated.

### **Recording Protocol**

All studies were intended to last for 2 days, during which time pH data were received and stored in the receiver. Patients were encouraged to engage in their usual activities including going to work, exercising, and socializing. Except for the requirement of eating at least one high fat meal each day, there were no dietary guidelines. Consumption of alcoholic beverages was neither encouraged nor prohibited. Study subjects were asked to keep a diary documenting food intake, periods of sleep, and occurrence of symptoms. When showering, subjects were instructed to leave the data receivers outside but as close as possible to the shower such as on the bathroom floor or toilet. The maximal range of the receiver was 3–5 feet.

After 48 h, patients returned to the GI laboratory, where they turned in their receivers and diaries. In addition, at the conclusion of the study a subset of patients at the Cleveland Clinic Foundation (14 GERD patients and 15 asymptomatic controls) who underwent Bravo monitoring, as well as a comparator group of 30 consecutive age- and sex-matched symptomatic patients who underwent conventional ambulatory esophageal pH monitoring with a transnasal catheter. They also completed a questionnaire addressing their satisfaction with the overall study using a 6-point visual analog scale (0 = very satisfied, 5 = never do again), along with a yes/no assessment of discomfort and interference with activities of daily living (diet, sleep, activity level). Eight days after the completion of the study, a chest x-ray was obtained for each subject to confirm pH capsule dislodgment. For patients with persistent capsule attachment at 10 days, another chest x-ray was performed 5 days later (or a total of 15 days from start of study). If a subject demonstrated failure of spontaneous pH capsule detachment on the day 15 x-ray, endoscopic dislodgment of the probe was undertaken.

### **Data Analysis**

When recording was completed and the receivers were returned, the pH study data were uploaded to a computer via Datalink (Medtronic), which is compatible with Windows 95/98/2000 NT (Microsoft, Redmond, WA). Temporal food intake, symptom, and supine period data extracted from the subject diaries were manually merged with the pH recording data. The receiver has an event marker available; however, this was not used for the current study. A summary of the pH data were then generated including a pH tracing and statistics on the total time and percentage of time with pH <4.0, the longest episode during which pH was <4.0, the total number of reflux episodes, the number of episodes during which pH was <4 for 5 min or more, the total duration of pH recording, total time and percentage of time upright, supine, and postprandial reflux. Data from the satisfaction questionnaire was reported on a 6-point visual analog scale

(0 = very satisfied, 5 = never do again). Discomfort was assessed as either present or absent, and alteration of daily activities was assessed as either none or mild restriction *versus* moderate or severe restriction.

Esophageal acid exposure data among subjects are summarized by median values and either 95th percentile values or ranges, given that the data were not normally distributed. The SE of the 95th percentile is equal to 2.18 times the SD divided by the square root of the sample size. Based on an SD of 2% (pilot data), the SE of the 95th percentile in sample sizes of 30, 60, and 100 would be 0.79, 0.56, and 0.44, respectively. Parameters of pH such as reflux events are summarized as mean  $\pm$  SEM. Recording efficacy comparison between the 4-cm antenna receiver system and the 7-cm antenna receiver system are also summarized as mean  $\pm$  SEM. Questionnaire data assessing satisfaction and comfort with the Bravo system and catheter-based system are also summarized as a mean  $\pm$  SEM. Median data are compared using a paired nonparametric test. Averaged data are compared using the Student's *t* test. A value of  $p < 0.05$  was considered significant.

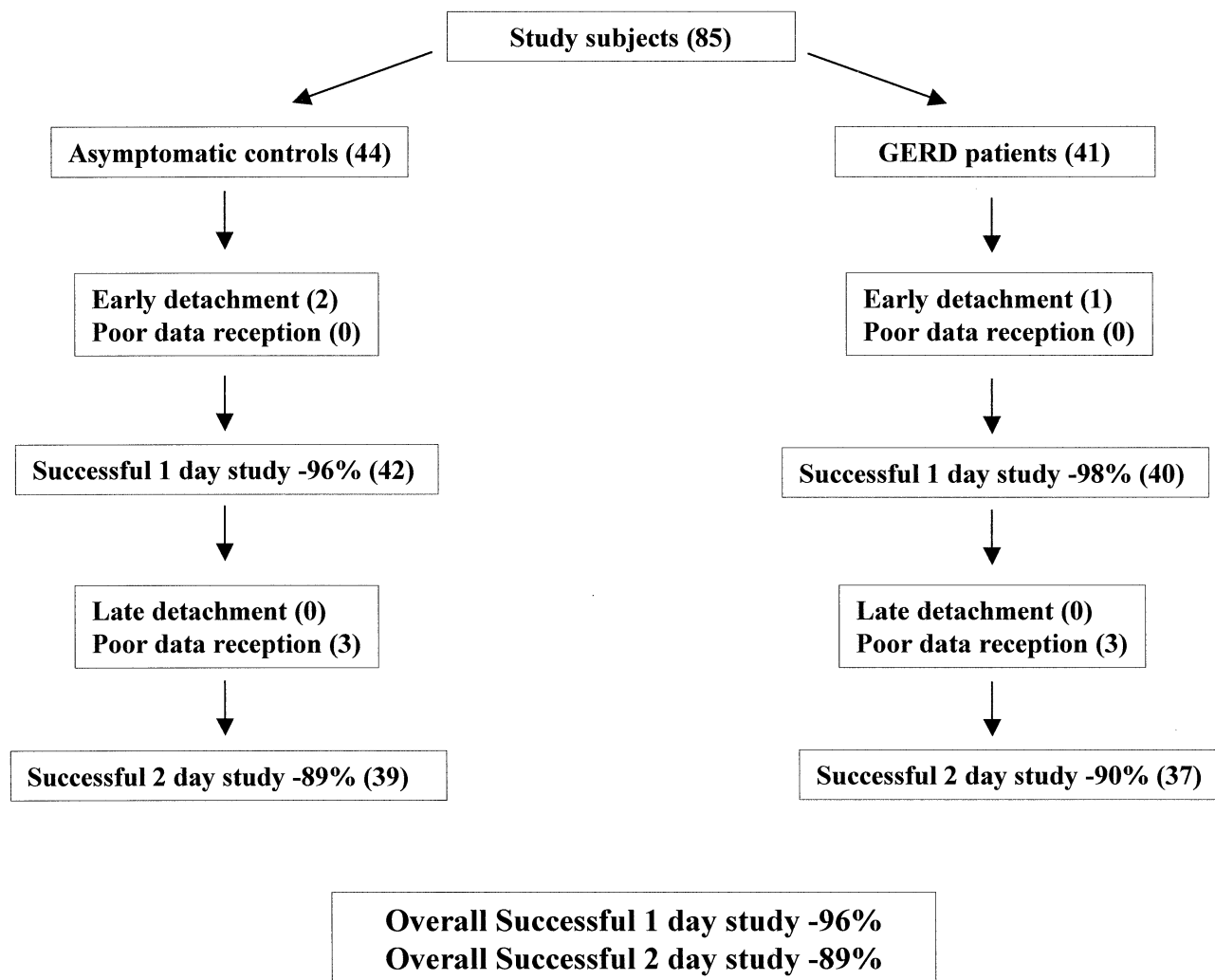
## **RESULTS**

### **Attachment Efficacy, Safety, and Tolerability**

Placement of the pH capsule was successful in all subjects. Two subjects required a second capsule to be placed during the initial procedure because the first failed to detach from the introducer assembly. Of the 85 subjects, 23 (27%) did not request or require sedation for capsule placement.

The pH capsules were generally well tolerated, with only two subjects experiencing discomfort to the extent that they requested it be removed immediately upon completion of the 2-day recording. One capsule needed to be removed endoscopically because of failure to spontaneously detach within 15 days. The three capsules were removed endoscopically by grasping the capsule with biopsy forceps and pushing it off the mucosa. Most subjects noted a mild foreign body sensation (especially while eating), and four had moderate chest pain that resolved once the capsule detached.

Overall subject satisfaction with the procedure was significantly better in the Bravo group compared to the conventional nasal system ( $0.8 \pm 0.1$  vs  $1.9 \pm 0.2$ , respectively,  $p < 0.001$ ). The conventional system was associated with significantly more throat discomfort (22 of 30 vs four of 29,  $p < 0.001$ ) compared to the Bravo system. However, there was significantly more esophageal discomfort in the Bravo group than with the conventional system (10 of 29 vs five of 30,  $p < 0.05$ ). This esophageal discomfort was significantly more common in the controls (nine of 14) than in the GERD patients (one of 15) ( $p = 0.002$ ). Daily routines were changed in none of 29 subjects in the Bravo group *versus* 11 of 30 in the conventional group. Both diet and activity were significantly affected (diet, 47% vs 3%,  $p < 0.001$ ; activity, 60% vs 0%,  $p < 0.001$ ) in the conventional group compared



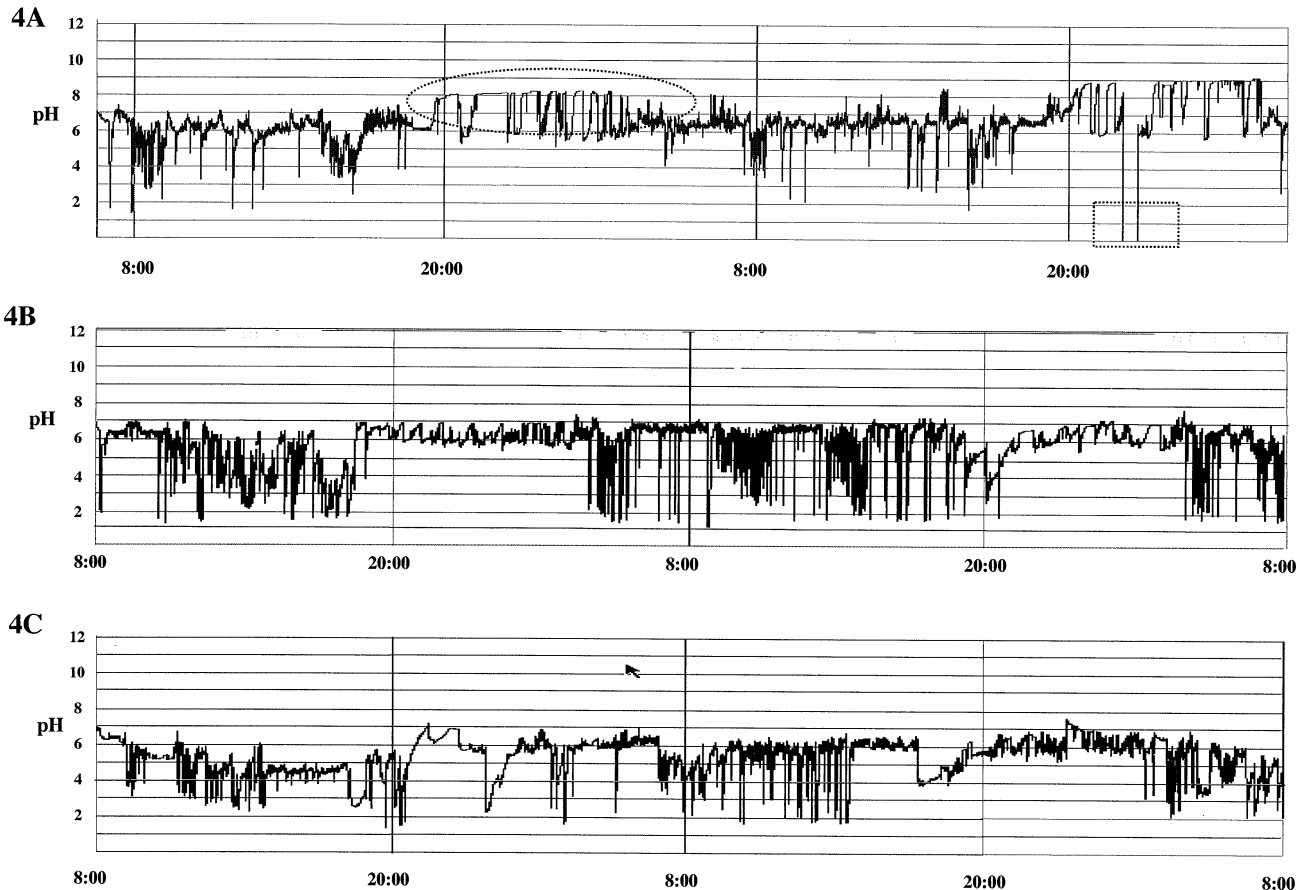
**Figure 3.** Recording efficacy of the Bravo pH monitoring system. Three early detachments occurred during the first 24 h. During study day 2 there was poor data reception in six subjects. This may be due either to technical malfunction of the receiver or to the receiver being out of range of the pH capsule.

to the Bravo group, respectively. There was no systematic effect on sleep patterns between the two pH monitoring systems; disrupted sleep was reported in two of 22 in the Bravo group and nine of 30 in the conventional group. All 12 GERD subjects who were unable or unwilling to undergo conventional esophageal pH monitoring completed the 48 h study without difficulty or complications.

#### **Recording Efficacy**

Interpretable pH recordings of at least 16-h duration were obtained in 82 of the 85 subjects. The three subjects with recordings of <16 h had premature capsule detachment. Interpretable pH recordings of at least 36 h duration were obtained in 76 of the 85 subjects. Seven subjects had inadequate data reception resulting in <18 h of data capture during day 2 despite continued capsule attachment (Fig. 3). Periods of time during which data capture was interrupted were indicated on pH tracings by gaps. Such gaps could

potentially be attributable to technical malfunctions in any of the electronics or to the receiver being beyond the range of the signal emanating from the pH capsule. During the 8 months that these studies were conducted, two major modifications were made to the hardware to reduce data loss: 1) a 7-cm antenna was added to the receiver to improve reception, and 2) the electronic board in the pH capsule was changed from ceramic to fiberglass to improve carrier frequency stability. Of the 85 subjects initially enrolled in this study, 15 subjects (eight controls and seven GERD patients) had studies performed with the 4-cm antenna and ceramic electronic board, whereas 70 subjects (36 controls and 34 GERD patients) had studies performed with the modifications. The impact of these modifications was evident by comparing the rate of mean data capture before the modifications ( $95\% \pm 3.5\%$  of pH data points) to that experienced with the modified equipment ( $98\% \pm 1\%$  of pH data points) ( $p < 0.05$ ). Examples of pH tracings obtained using



**Figure 4.** (A) Forty-eight-hour pH tracings using the Bravo pH monitoring system in a normal subject. The elevated baseline in the supine portion of the study (delineated by circle) represents drying out of the probe during sleep. In contrast to the classic pseudoreflux pattern seen with standard catheter-based pH monitoring, this software reports periods of drying out as an elevated baseline. There is also a small area of data dropout (delineated by square) representing a period during sleep when the patient rolled away from the receiver and away from the signal emanating from the pH capsule. Of note, the software does not record this artifact as a pH drop <4. (B) Forty-eight-hour pH tracings using the Bravo pH monitoring system in a GERD patient with upright reflux. Data capture is excellent. (C) Forty-eight-hour pH tracings using the Bravo pH monitoring system in a GERD subject with combined upright and supine reflux.

the most current hardware are illustrated in Figure 4 (normal, upright, combined).

**Esophageal Acid Exposure Values**

Esophageal pH parameters during the initial 24-h study period in the two study groups are illustrated in Table 1. The

GERD patients had a significantly greater percentage of time that pH was <4 than controls during the upright, supine, and total periods of study, as well as the total reflux events and episodes of reflux >5 min (*p* < 0.05). Esophageal pH data from the patients finishing the 2-day study are

**Table 1.** Esophageal Acid Exposure Data Obtained During the First 24 H of Recording With the Wireless pH Recording System

pH Parameter	Controls (n = 42)	GERD Patients (n = 40)
	Median (95th Percentile)	Median (Range)
pH <4, Total	2.3% (5.9%)	6.5% (0.8–27.6%)*
pH <4, Upright	3.2% (7.8%)	7.7% (1.4–29.0%)*
pH <4, Supine	0.1% (6.3%)	1.7% (0.0–23.9%)*
Reflux events (mean ± SD)	40.9 ± 23.0	83.2 ± 42.8*
Events >5 min (mean ± SD)	1.4 ± 1.3	4.7 ± 4.7*

Values for numbers of reflux events and reflux events persisting for >5 min are normalized to reflect what they would equal in 24-h recordings.

\* *p* < 0.05 vs control.

**Table 2.** Esophageal Acid Exposure Data Obtained During the Entire 36–48 H of Recording With the Wireless pH Recording System

pH Parameter	Controls (n = 39)	GERD Patients (n = 37)
	Median (95th Percentile)	Median (Range)
pH <4, Total	2.0% (5.3%)	6.6% (1.0–21.7%)*
pH <4, Upright	2.6% (6.9%)	7.6% (1.3–27.7%)*
pH <4, Supine	0.5% (6.7%)	3.2% (0.0–24.5%)*
Reflux events (mean ± SD)	36.8 ± 20.1	80.2 ± 39.4*
Events >5 min (mean ± SD)	1.2 ± 0.55	2.14 ± 3.5*

Values for the number of reflux events and reflux events persisting for >5 min are normalized to reflect what they would equal in 24-h recordings.

\* *p* < 0.05 vs control.

**Table 3.** Comparison of the Esophageal Acid Exposure Data Obtained During Days 1 and 2 in the Subset of Controls and GERD Patients With 2 Evaluable Days of Recording

	Controls (n = 39), Median (95th Percentile)		GERD Patients (n = 37), Median (Range)	
	Day 1	Day 2	Day 1	Day 2
pH <4, Total	2.2% (5.8%)	1.8% (6.6%)	6.6% (0.8–27.6%)	7.7% (0.9–28.6%)
pH <4, Upright	2.9% (6.8%)	2.4% (7.3%)	7.9% (1.40–29.1%)	7.2% (1.1–31.1%)
pH <4, Supine	0.0% (6.7%)	0.2% (8.8%)	1.2% (0.0–23.9%)	1.5% (0.0–45.5%)

No significant difference was found in either group for any parameter between day 1 and day 2.

illustrated in Table 2. Values of esophageal acid exposure for 36–48 h are only marginally different from those shown in Table 1 for the first 24 h of recording. Examining the values in Tables 1 and 2, the most atypical for the control population is the range observed for supine reflux. This extended range is attributable to four outlier values (9.23%, 10.2%, 18.2%, and 18.6%). Review of the diary data in these four subjects revealed that they had eaten highly reflux-provoking diets within 1 h of sleep. Elimination of these outliers defined a median supine percentage of the time that pH was <4 of 0.3% (95th percentile, 3.2%) and a median total percentage of the time that pH was <4 of 2.0% (95th percentile, 4.9%).

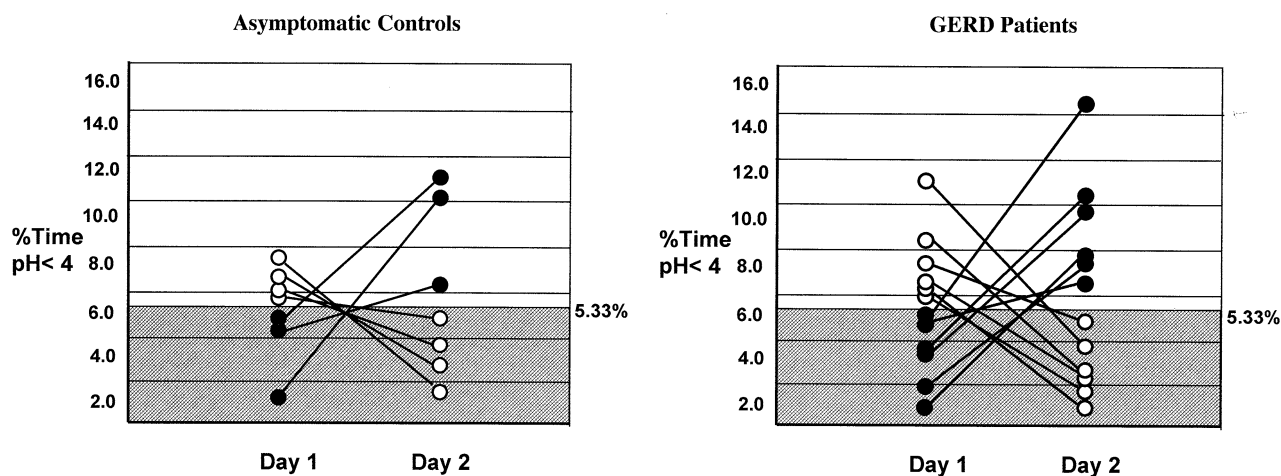
#### Day-to-Day Variability in Esophageal Acid Exposure Values

A total of 39 control subjects and 37 GERD patients had interpretable recordings for 2 consecutive days, offering an opportunity to examine day-to-day variability in esophageal acid exposure values and to see whether an extended recording period improved the power of the test to discriminate the GERD population from normal. The overall acid exposure values from day 1 are compared to those obtained from day 2 in Table 3, with no significant difference between the days. However, 12 GERD patients and seven control subjects had a normal esophageal acid exposure

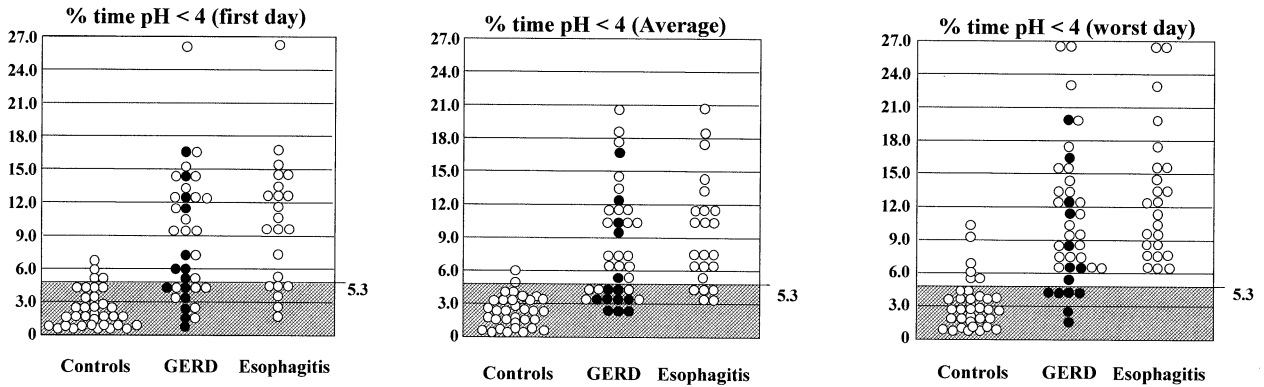
value on 1 day and an abnormal exposure on the other. Half of these were abnormal on day 1 and half on day 2 (Fig. 5). Thus, the potential added diagnostic yield of the extended recording period was best illustrated by comparing the results of the first days recording to those of the worst day of recording (Fig. 6). As evident in the figure, either when considering the GERD population as a whole or, even more so, when considering the subset of the GERD population with a history of esophagitis, an increased proportion of these individuals demonstrated abnormal acid exposure on 1 of the 2 days of recording. Table 4 compares the sensitivity, specificity, positive predictive value, and negative predictive value of the test when analyzed by the results of the entire study, on day 1, or on the worst day in terms of acid exposure using the 5.3% value as the upper limit of normal.

#### DISCUSSION

The major finding of this study was that successful 24-h ambulatory pH studies were obtained in 96% of volunteer subjects and patients using a novel wireless esophageal pH recording system. Evaluable 2-day recordings were obtained in 89% of enrolled subjects. The technical performance of the system was good, improving from capture of 95% of pH data point with an earlier design to 98% with the current



**Figure 5.** Day-to-day variability of total percentage of the time that pH was <4 in asymptomatic controls and GERD patients. Using 5.33% as our upper limit of normal for total percentage of the time that pH was <4, three to four asymptomatic controls (depending on the day) and six GERD patients may have been misclassified if the study was limited to a single day. (○), subjects with abnormal readings on day 1; (●), subjects with abnormal readings on day 2.



**Figure 6.** Comparison of the results from day 1 data (left), days 1 and 2 data (center), and the worst day data (right). The worst day data analysis considers a test to be positive if there is an abnormal result on either or both days, and a test to be negative if the results are normal on both days. Considering the GERD population as a whole or, even more so when considering the subset of the GERD population with a history of esophagitis, an increased proportion of these individuals demonstrated abnormal acid exposure on 1 of the 2 recording days. Two other normal subjects would be considered abnormal if worst day data were evaluated. (●) in the GERD population represent endoscopy negative patients.

design. Placement of the pH capsules was accomplished by referencing to endoscopic landmarks (6 cm proximal to the squamocolumnar junction) to approximate the conventional position of 5 cm proximal to the upper margin of the

manometrically defined LES. The attachment procedure was easily learned and, inclusive of the upper endoscopy, was typically completed in less than 10 min. No significant complications occurred; however, three probes had to be removed endoscopically, two because of discomfort and one because of failure to spontaneously detach within 14 days. Compared to traditional pH testing, wireless pH monitoring caused significantly less impairment of daily activities and less throat discomfort. Of note, 12 patients who were either unwilling or unable to undergo a conventional catheter-based pH monitoring study successfully completed a 48-h study with the wireless system.

**Table 4.** Power of the 2-Day Study in Distinguishing Control Group From GERD, Esophagitis, and ENRD Groups When Analyzed Using Results From Entire Recording Period, Day 1 of Recording, or Worst of 2 Days of Recording

	Control Group vs Entire GERD Group (n = 37)		
	Both Days	Day 1	Worst Day
Normal/abnormal	13/24	12/25	6/31
Sensitivity	64.9%	67.5%	83.8%
Specificity	94.8%	89.7%	84.5%
Positive predictive value	92.3%	86.2%	83.8%
Negative predictive value	74.0%	74.5%	84.6%

	Control Group vs Esophagitis Group (n = 23)		
	Both Days	Day 1	Worst Day
Normal/abnormal	5/18	6/17	0/23
Sensitivity	78.3%	73.9%	100%
Specificity	94.8%	84.5%	84.5%
Positive predictive value	90.0%	73.9%	79.3%
Negative predictive value	86.0%	84.6%	100%

	Control Group vs ENRD Group (n = 14)		
	Both Days	Day 1	Worst Day
Normal/abnormal	9/5	6/8	6/8
Sensitivity	35.7%	57.1%	57.1%
Specificity	94.8%	84.5%	84.5%
Positive predictive value	71.4%	66.7%	57.1%
Negative predictive value	80.4%	85.3%	84.6%

In all analyses, the 95th percentile value of the control group for the entire study period (5.3%) was used as the upper limit of normal. Using that value, two, four, and six of the 39 controls would had abnormal esophageal acid exposure values for the entire study, day 1, and the worst day, respectively. ENRD = Endoscopy negative reflux disease.

Esophageal acid exposure is known to be dependent upon several factors including diet, activity, and the position of the pH electrode relative to the stomach. A major objective of this study was to determine normal values for esophageal acid exposure using the wireless pH recording apparatus in asymptomatic control subjects with unrestricted activity and consuming a somewhat reflux-provoking diet inclusive of at least one fatty meal daily. As detailed in Tables 1 and 2, our findings were that the 95th percentile value of distal acid exposure (defining the upper limit of normal) was 5.9% for the first 24 h and 5.3% for the entire study period. These values are slightly greater than those previously reported using conventional pH electrodes and recording systems; those reported values range from 3.4% to 5.8% (7–10). Our suspicion is that the increased acid exposure values observed are a consequence of the less restrictive recording conditions during which subjects engaged in unmodified daily activities and were free to consume an *ad libitum* diet with the only proviso being the inclusion of at least one high fat meal. This suspicion is supported by the fact that four of the outlier controls with the highest total and supine percentage of the time that pH was <4 had eaten highly refluxogenic diets within 1 h of sleep. It is recognized that recording periods obtained with catheter-based pH elec-

**Table 5.** Sensitivity and Specificity of the Wireless pH Recording System in Distinguishing the Subset of GERD Patients With a History of Esophagitis From Controls

	Day 1	Worst Day	Vitale (11)	Johnsson (7)	Mattioli (12)	Masclee (13)
Sensitivity	74%	100%	77%	87%	92%	91%
Specificity	90%	85%	91%	97%	100%	85%

Data are shown for day 1 and for the worst of the 2 recording days using 5.3% as the upper limit of normal.

Author names and references are the study where those sensitivity and specificity data are cited.

trodes are often associated with restrictions in both diet and physical activity, thereby decreasing reflux-provoking circumstances (2).

Consistent placement and positioning of the pH electrode is an important methodological detail in esophageal pH monitoring. Historically, the convention of positioning the electrode 5 cm proximal to the upper margin of the LES was selected because it was distant enough from the stomach to minimize the potential for inadvertently becoming repositioned within the stomach in the course of the study (swallow-related movement, confounding effects of hiatus hernia, etc.) and yet close enough to the stomach to sample the region of esophageal mucosal most adversely affected by gastroesophageal reflux (1). We elected not to use manometric landmarks for pH capsule placement, reasoning that endoscopically directed placement is simpler and that a relatively constant relationship exists between the axial position of the squamocolumnar junction and the physiological sphincter. Previous analysis of both normal controls and patients with hiatus hernia using concurrent manometry, fluoroscopy, and an endoscopically placed metal clip marking the position of the squamocolumnar junction demonstrated that the upper margin of the LES was uniformly 1–1.5 cm proximal to the squamocolumnar junction (6). It was on this basis that we selected the position of 6 cm proximal to the squamocolumnar junction. In addition, precise positioning is probably less critical with this recording system given that the capsule is physically attached to the mucosa, virtually guaranteeing that a constant position relative to the squamocolumnar junction will be maintained throughout the study period. Ultimately, however, the validity of this placement method is evident in the data obtained using it. As shown in Table 4, the discriminative power of the test in distinguishing a reflux population from a control group was very comparable to values obtained using conventional pH electrodes and recording methods (7, 11–13).

As alluded to above, the power of the wireless pH recording system in discriminating a GERD population from controls was comparable to that observed in previous studies (7, 11–13). In fact, most prior studies have examined the discriminative power between esophagitis patients and controls. A comparison of the sensitivity and specificity of the wireless pH study in distinguishing esophagitis patients from controls with that observed in previous studies is shown in Table 5. It is noteworthy that the discriminative power of the study is roughly comparable when analyzed by the results obtained from the first 24 h but the sensitivity is

actually improved when analyzed by the results obtained from the worst day of recording. This strategy of data analysis takes advantage of the observation that esophageal acid exposure can exhibit significant day-to-day variability (14). Illustrative of this, 12 of our GERD patients had abnormal acid exposure on 1 day and a normal value on the other. Thus, using data from the worst day of recording maximizes the sensitivity of the test.

The data evaluating the ability of the wireless pH system to discriminate endoscopy negative GERD patients from controls was also similar to previous reported studies (11–13). In contrast to esophagitis patients, there was no significant improvement in sensitivity or specificity when the analysis included results of the worst day of recording. This is likely secondary to the fact that abnormal esophageal acid exposure is only one of several potential etiological variables distinguishing the endoscopy negative population from controls. Patients with endoscopy negative reflux may be hypersensitive to acid reflux and symptoms may occur despite a normal physiological reflux profile (15). These patients could potentially be better detected with an analysis of symptom-reflux association. In this regard, the wireless pH monitoring system may be of benefit as the extended 48-h monitoring period would increase the likelihood of documenting relationships between atypical symptoms and reflux events. That would, however, require a much larger and more systematic analysis than was undertaken in this study.

In summary, the Bravo wireless ambulatory pH recording system is a well tolerated, reliable means of quantifying esophageal acid exposure. It is a viable option for patients who are unwilling or unable to undergo conventional ambulatory pH monitoring studies using a transnasally positioned pH electrode. Key potential advantages of the system relate to its versatility. Because the recording apparatus is unobtrusive and comfortable, a broader array of test paradigms can be explored. Flexibility is also added by the extended recording period. Our data suggest that when used for clinical purposes, this can increase the discriminative power of the test, and that this is maximized by using data from the worst of the 2 days with a normal range of 0–5.3%. Alternatively, the 2-day recording period can be leveraged to compare two experimental conditions within the confines of a single study or obtain a better assessment of symptom correlation over an extended period. Finally, use of a mucosally attached pH electrode virtually eliminates the possibility of recording artifact related to relative movement between the pH electrode and the mucosa in the course of

the study period. This opens the door to exploring the pH microenvironment of other endoscopically defined locations. Undoubtedly, these and further refinements in methodology will permit broader use of pH monitoring, with the hopeful consequence of improving both our understanding of the pathogenesis of acid-related disorders and our management of complex cases.

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