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Review

Evaluation of Gastroesophageal Reflux Disease Using the Bravo Capsule pH System

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Gastroesophageal reflux disease (GERD) is a disease predominantly seen in the West but there is a rising trend in Asia. Ambulatory 24-hour catheter-based pH monitoring has been the de facto gold standard test for GERD that correlates symptoms with acid reflux episodes. However, drawbacks such as patients' discomfort, and catheter displacement render the test as cumbersome and error-prone. The Bravo pH wireless system is designed to be user-friendly and has an added advantage of prolonged pH monitoring. The system is comparable to the catheter-based pH monitoring system in terms of diagnostic yield and symptom-reflux association. Indications include evaluation of patients with refractory GERD symptoms and prior to anti-reflux surgery. Bravo utilizes a wireless pH-sensing capsule with a complete prepackaged system, and a data processing software. The capsule may be positioned indirectly using endoscopic or manometric landmarks or under direct endoscopic guidance. Optimal threshold cut-off values are yet to be standardized but based on available studies, for the Asian population, it may be recommended for total % time pH < 4 of 5.8 over 48 hours. Cost is a limitation but capsule placement is relatively safe although technical failures may be seen in small percentage of cases.

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Key Words
Asia; Esophageal pH monitoring; Gastroesophageal reflux disease

Introduction

Gastroesophageal reflux disease (GERD) is on the increase in Asia with prevalence ranging from 5% up to 18%.[1] Heartburn and regurgitation are typical symptoms of GERD, but are unreliable in terms of distinguishing GERD from functional gastrointestinal (GI) diseases particularly among Asians.[2,3] In addition, the presence of reflux symptoms lack direct correlations with increased esophageal acid exposure, as well as endoscopically proven esophagitis.[2,3]

In a symptomatic Asian patient with normal endoscopic findings, the diagnosis of GERD would often rely on documented high esophageal acid exposure. Ambulatory 24-hour pH monitoring, first introduced in 1974, was developed to detect abnormal levels of acid reflux in the lower esophagus.[4,5] Conventional pH monitoring requires a nasopharyngeal catheter with pH electrode placed 5 cm above the lower esophageal sphincter to document distal esophageal acid exposure and correlate this with reflux symptoms.[5] Although highly sensitive and specific, several pitfalls with this procedure have been cited. Drawbacks include patient discomfort due to nasal and pharyngeal irritation from the pH catheter. Oftentimes, patients limit their daily physical activities and alter their diets, which may

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underestimate the amount of actual reflux episodes. Methodological difficulties such as incorrect placement and catheter migration have been observed which may affect test accuracy thus leading to erroneous results.[3,4,6]

A wireless pH capsule was designed and developed in 2003 to overcome these limitations.[7,8] The Bravo pH wireless capsule system (Given Imaging; Medtronic Inc, Shoreview, MN, USA) is a device that is temporarily implanted in the distal esophageal mucosa to avoid the inconvenience of wearing a nasopharyngeal electrode.[5,9] The diagnostic yield of Bravo system was comparable to the catheter-based system as seen in studies performed in both the Caucasians and Asian populations.[4,5] Symptom association with reflux episodes is likewise similar between the wireless and conventional pH monitoring systems.[9] More importantly, the Bravo capsule was observed to be significantly better than the conventional system in terms of tolerability with minor impact on diet and daily activities.[10,11]

Test Equipment

The Bravo pH monitoring system utilizes a wireless pH-sensing capsule. The prepackaged system is composed of the following (Fig. 1): pH receiver kit; capsule with delivery system, an internal battery and transmitter; vacuum pump; suction tubes; calibration stand, buffer solution; infrared receiver device; and software.[4,12] The capsule is oblong-shaped, measures 6 mm × 5.5 mm × 25 mm and has an antimony pH and reference electrode at its distal end.[7,12] The delivery system consists of an 80-cm long, 6-Fr diameter tubular device with measurement markings to identify catheter distance from the incisors.[13]

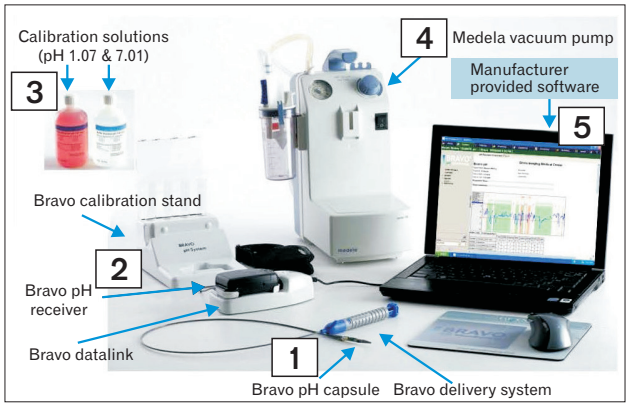

Figure 1. Components of the Bravo capsule system. Prepackaged system consists of (1) Bravo pH capsule with delivery system, (2) pH receiver kit, (3) buffer solution, (4) vacuum pump with suction tubes; and (5) manufacturer-provided software.

Prior to usage, the Bravo pH capsule is activated by a magnetic switch and requires pH calibration. The capsule is submerged in a buffer solution of pH 7.01 for at least 10 minutes, at room temperature, calibrated, rinsed, and then recalibrated in the second buffer solution of pH 1.07. The receiver hardware is also checked to confirm proper data transmission.[14] The carrier frequency of the pH signal is in the 433-MHz band.[12] Digital data transmission occurs every 12 seconds with 2 pH data-points obtained every 6 seconds.[12,15] The average battery-life of a Bravo capsule may be up to 14 days.[16]

Test Procedure

Prior to the test, medications such as proton pump inhibitors (PPIs) and H2-blockers should be discontinued for 14 days and at least 3 days respectively.[5,10] Antacids should be stopped 24 hours before the study.[17] Patients are instructed to fast for 6 hours prior to the procedure. Upper endoscopy is usually performed to guide placement of the capsule either through conventional or direct guidance.

After activation and calibration, connect the vacuum tubing to the Bravo delivery device and perform vacuum pump check to verify gauge reaches 700 mmHg. The Bravo capsule can be inserted through the nostril or mouth while the patient is in a left lateral decubitus position. Oral insertion is preferred compared to transnasal insertion due to difficulty in passing the delivery system through the angles of the nasopharynx.[15] With conventional endoscopic guidance, the gastroesophageal junction (GEJ) is identified, followed by removal of endoscope and then the capsule is placed 6 cm proximal to the GEJ.[12,14] This position is derived from observation that the high pressure zone of lower esophageal sphincter (LES) is typically 1 to 1.5 cm proximal to the GEJ. With direct endoscopic guidance, the endoscope is left in place within the esophagus while the Bravo delivery system is being deployed and capsule placed under direct view of the endoscope.[18] Direct-guidance has been shown to be equally effective as conventional-guidance with the added advantage of avoiding a second endoscopy to confirm the placement.

More recently, manometry-guided placement has been shown to be equally suitable.[19] With manometry guidance, the Bravo capsule is positioned at 5 cm above the proximal border of the LES if delivered transnasally.[4,9,10] Alternatively, the Bravo capsule is better delivered orally because of tolerability, and by using a correction factor of 4 cm for the difference between oral and nasal intubation. A retrospective study suggests that manometry placement may be better since endoscopic placement resulted in higher acid exposure on day one and the cost might be higher.[19] Furthermore, capsule

misplacement with endoscopy is common especially more proximal displacement, however, misplacement is not necessarily associated with poor pH results.[20]

Once it is in the correct position, the vacuum pump is used to apply suction to the wall of the capsule. A vacuum pressure of more than 510 mmHg for 15 to 30 seconds is required for successful deployment, although 700 mmHg is usually recommended by the manufacturer.[8,9,11,12] The activation button is pressed to deploy a spring-loaded, stainless-steel pin to attach the capsule to the mucosa. The activation button is then turned clockwise at 90° to release the capsule from the delivery system.[12] Lastly, the data receiver is then attached to a belt around the patient's waist.[7,9] During bath or sleep, the receiver should be within 3 to 5 feet of the patient for successful transmission.[12,15] Figure 2 illustrates the steps in capsule placement.

Patients are instructed to keep a daily diary to log their symptoms, meals, and sleep. Acidic drinks such as coffee, soda, cranberry, and orange juice should be avoided.[15] Subjects are encouraged to perform their regular daily physical activities during the test.[14] Data recording and storage of pH data typically occur over 48 hours.[1]

Analysis of Bravo pH Data

The data obtained from the capsule are recorded and processed by the manufacturer provided software.[9] Patients' diary entries and other temporal data are entered manually using the software.[12] The parameters measured are: percent of total time of pH < 4; the total number of reflux episodes in both the upright and supine positions; duration of reflux episode; the number of reflux episodes longer than 5 minutes; symptom score; and the mean duration of reflux episodes.[6,9,12] A reflux episode is defined as a drop in pH below 4 lasting for ≥ 10 seconds.[13]

Compared with traditional 24-hour catheter-based pH monitoring, the Bravo pH data can be recorded for 48 hours or more. Esophageal acid exposures for the first day, second day and combined 48 hours are calculated separately.[10] In patients who underwent endoscopic guidance under sedation, it has been proposed that to eliminate the effects of sedatives on the LES, the first 6 hours of pH data should be excluded in the analysis of results.[10]

There is day-to-day variability in acid exposure and therefore an extended recording beyond 24 hours may be preferable.[10] Ang et al[5] compared Bravo pH monitoring with that of conventional pH catheter but the mean acid exposure time was not significantly different. However, the Bravo capsule seemed to have recorded fewer reflux episodes, a finding similar to a previous study by Varannes et al.[9] Acid exposure values were found to be 1.2% greater with the catheter system compared to the Bravo system.[5,9] Extended monitoring becomes of value in this case and Ang et al[5] noted a 61% positive diagnostic yield with an incremental diagnostic yield of 30% seen at 48-hour period. Moreover, monitoring can be extended up to 96 hours to increase the chance of detecting reflux events and to establish symptom association.[5] Therefore, it can be used to evaluate medications responses or to document acid reflux in patients with refractory symptoms despite therapy.[15]

To assess the temporal relationship between acid refluxes and symptoms, the patient's symptom index score (SI), symptom sensitivity index (SSI) and symptom association probability (SAP) are utilized. SI, first described by Wiener et al[19] in 1988, is defined as the number of times reflux symptoms occured when pH was < 4 divided by the total number of symptoms reported multiplied by 100. SSI refers to the percentage of symptom-related reflux episodes while the SAP pertains to a statistical parameter calculated to quantify the likelihoods that the patient's symptoms are related to reflux. Significant symptom-reflux association occurs when the SSI

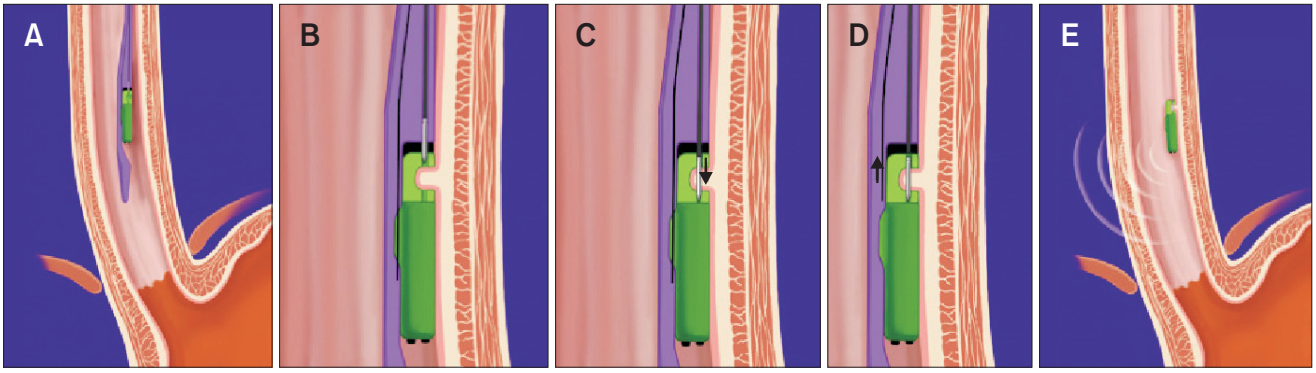

Figure 2. Steps in placement of the Bravo capsule. (A) Position Bravo pH capsule. (B) Apply suction to catheter until 700 mmHg is reached for 60 seconds. (C) Depress plunger to advance pin. (D) Release capsule by rotating the plunger clockwise. (E) Begin pH recording.

is ≥ 10%, SI is ≥ 50%, and SAP is > 95%.[6,13]

Results

An abnormal composite pH score is the most accurate method to identify presence of GERD.[21] However, optimal threshold cut-off values are yet to be standardized. Penagini et al[11] in 2007, explained that a pH monitoring study is considered normal when esophageal acid exposure is in the normal range and the SI is less than 0.5.

A pathological esophageal acid exposure in overall 48-hour duration is characterized by the total percentage of time pH < 4 greater than 5.3% according to Pandolfino et al (Table 1).[22] Later, Ayazi et al[2] described greater than 4.9% for the total percentage of pH < 4 over 48-hour period but Wenner et al[23] defined an abnormal esophageal acid exposure as > 4.4% after 48-hour (Table 1).[23] The presence of an abnormal composite pH score in either the first or second 24-hour had a sensitivity of 93% but specificity and positive predictive value of 100% for a diagnosis of GERD.[21]

On the other hand, there is limited data on normal pH thresholds from Asia compared to the West. In a recent study by Ang et al,[7] they determined the following data in a cohort of Singaporeans (age range 22-50, with two-thirds males and two-thirds of Chinese ethnicity): total percentage time pH < 4 at 24 hours was 7.4%, at 48 hours was 6.3% and overall 48 hours study was 5.8% (Table 1).[7] Besides ethnicity, the differences between Ang et al[7] and other reported Western studies could be due to unequal gender and age distribution. More studies are needed from Asia to confirm and to compare the findings with those from the West. Based on the above observations, for now in Asia, the recommended normal values for total percentage of time pH < 4 would be close to those reported by Ang et al,[7] that is < 7.4% at 24 hours, < 6.3% at 48 hours, and < 5.8% for overall 48 hours. However, it is our view that the 24-hour pH value of < 7.4% was too high, and we recommend a lower level, similar to what was reported by Pandolfino et al,[22] that is < 5.8%. .

Indications

In 2005, the United States Food and Drug Administration approved the use of Bravo pH monitoring system for the evaluation of patients with GERD. The American Gastroenterology Association also approved the use of Bravo capsule for documenting adequacy of PPI therapy in Barrett's esophagus and to evaluate atypical symptoms unresponsive to PPI therapy.[15]

Table 2 summarizes the clinical uses of the capsule monitoring system.

Many gastroenterologists in Asia often face the dilemma in choosing the appropriate pH diagnostic tools. In the ideal situation where cost is not an issue, we would recommend Bravo capsule for its better tolerability, and for its ability to evaluate the efficacy on-PPI. If cost is an issue then pH probe is recommended for exclusion of GERD off-PPI. For non-acidic reflux detection, the pH-impedance probe is clearly superior over both pH alone and Bravo capsule. Besides, the pH-impedance probe can be performed both off- and on-PPI, and the study duration for pH-impedance can be potentially extended beyond 24 hours. However, besides cost, tolerability is an issue with the pH-impedance probe.

Relative contraindications to the use of Bravo capsule include pregnant patients, history of underlying bleeding diathesis, the presence of esophageal strictures, varices, diverticula and severe esophagitis with intestinal metaplasia.[5,12] Likewise, patients with previous

Table 2. Indications for Esophageal pH Testing Using the Bravo Capsule System (Adapted from Lacy et al,[3] Ang et al,[5] and Pandolfino and Kwiatek[15])

1. Evaluation of patients with GERD and normal EGD
2. Patients considered for endoscopic or surgical reflux therapy
3. Patients with typical GERD symptoms who fail empiric PPI therapy
4. Patients with atypical symptoms who fail empiric PPI therapy
5. Alternative for patients who cannot tolerate catheter-based monitoring

GERD, gastroesophageal reflux disease; EGD, esophagogastroduodenoscopy.

Table 1. Threshold Values of Esophageal Acid Exposure Using Bravo pH Readings

	Pandolfino et al[22] (2003)	Wenner et al[23] (2005)	Ayazi et al[2] (2009)	Ang et al[7] (2013)	Recommended normal Asian values
	Median (95th percentile)				
Total % time pH < 4 at 24 hours	2.2 (5.8)	0.7 (3.3)	1.1 (6.3)	1.7 (7.4)	< 5.8
Total % time pH < 4 at 48 hours	1.8 (6.6)	1.0 (0.6)	1.2 (5.9)	1.5 (6.3)	< 6.3
Overall 48-hour duration	2.0 (5.3)	0.8 (4.4)	1.4 (4.9)	1.9 (5.8)	< 5.8

upper GI surgery, history of Zollinger-Ellison syndrome, active malignancy or Crohn's disease are not recommended for this procedure.[5] Other contraindications include presence of a pacemaker or defibrillator which may interfere with signal transmission.[12,13]

Other Clinical Utility

In the pathophysiology of GERD, many patients develop reflux symptoms in the post-prandial state but this is a paradox since meals buffer the stomach acid.[16] An area of the proximal stomach distal to the squamocolumnar junction (SCJ) eludes the buffering effect of meals, the so-called "acid pocket," and studies have found an association between acid pocket and GERD. In this regard, measuring intragastric pH in this acid pocket using the Bravo wireless capsule system may be useful. Pandolfino et al[17] demonstrated that concurrent measurement of esophageal pH (6 cm proximal to the SCJ) and gastric pH (1.5 to 2 cm distal to SCJ) using 2 Bravo capsules was feasible and reliable.[16] Study results showed that the median pH of the cardia were significantly lower than the median esophageal pH during reflux events, which is compatible with an acid pocket.[17] Another study done by Ono et al[16] showed that the Bravo capsule, attached with multiple hemoclips at the greater curvature of the gastric body, can monitor treatment responses while on histamine receptor blockers.

In the evaluation of patients with non-cardiac chest pain (NCCP), pH monitoring may also be advantageous especially when they are unresponsive to a therapeutic trial of PPI. Karamanolis et al[24] reported that among 32 patients presenting with NCCP, over 60% had evidence of a pathological esophageal acid reflux and positive symptom index, specifically with the use of 48-hour Bravo pH monitoring.[24]

Trouble-shooting and Potential Complications

The Bravo capsule is usually well-tolerated and a successful capsule deployment is seen in 98% to 100% of cases.[12,15] After capsule placement, some subjects may experience throat discomfort, bleeding, odynophagia, dysphagia or mild foreign body sensation with eating, and chest discomfort.[4,8,12] Throat discomfort is seen less in the Bravo system compared to a catheter-based system but esophageal discomfort was reportedly more common with the capsule.[15] In the presence of severe odynophagia and chest pain (< 2% of cases) after capsule placement, a chest x-ray is essential to rule out perforation.[8,15]

Technical failures may occur in up to 15% of cases.[21] These include poor data transmission (4.5%), attachment failure (3.4%), early capsule dislodgement (4.5%), and detachment failure (1.5% to 6.8 %).[12,21] The need for capsule removal was seen in 6% of cases, and it may be indicated in patients with intolerable and persistent chest discomfort.[21]

Complications, such as GI bleeding and perforations, although rare, have been reported.[6] A capsule is considered to be detached from the esophagus when the pH suddenly drops below 2 followed by a sudden increase in pH > 6 which corresponds to capsule passage through the bowel.[9,11] The capsule usually detaches within 5 days. In cases where capsule failed to detach within 5 days as confirmed from radiological identification, endoscopic retrieval may be warranted.[21] Removal is performed by applying gentle pressures to the capsule using the tip of an endoscope to dislodge the capsule followed by its retrieval.[13]

Limitations

The cost is an important consideration especially in the Asian developing countries. A complete Bravo system costs around $25 704. A single-use Bravo capsule with delivery device costs $225 compared to the conventional trans-nasal pH catheter which costs $62.[12] In addition, standardized thresholds for abnormal esophageal acid reflux in Asia are lacking and the optimal recording periods is still in question. Furthermore, a higher rate of technical failures among inexperienced operators and associated chest pain symptom needing removal are other limitations to consider.

Conclusion

The Bravo pH monitoring system is a safe and well-tolerated alternative to the catheter-based pH monitoring. It is patient-friendly with the ability for prolonged pH recording. The Bravo capsule is recommended in the evaluation of patients with refractory GERD, prior to antireflux surgery, and monitoring of patient responses during therapy. Optimal threshold values have yet to be standardized particularly in Asia and prospective studies are still required to formulate appropriate interpretation guidelines.

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manuscript.

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