Wireless Capsule pH Monitoring: Does It Fulfil All Expectations?

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Key Words

pH monitoring • Wireless pH monitoring • Wireless capsule • Bravo capsule

Abstract

pH monitoring has been used as a diagnostic tool in gastro-oesophageal reflux disease (GERD) for many years. Recent studies have shown that wireless capsule pH monitoring is better tolerated and interferes less with daily activities as compared to traditional catheter-based pH monitoring. Moreover, prolonged recording time (48 h instead of 24 h) is possible with wireless pH monitoring. The main secondary effect of wireless capsule pH monitoring is induction of thoracic discomfort in 10–65% of the patients, which can vary from mild foreign body sensation to severe chest pain. Sensitivity and specificity of wireless capsule monitoring is comparable to that of traditional pH monitoring. It has not been proven yet that better tolerability and a longer recording time increases the diagnostic yield of wireless capsule monitoring in GERD.

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Introduction

The main indication for pH monitoring is in patients with persistent typical or atypical symptoms of gastro-oesophageal reflux disease (GERD) under acid-suppressive therapy. The inconveniency of traditional ambulatory 24-hour pH monitoring is, however, the need of a naso-oesophageal catheter which is generally not well tolerated, and results in a changed lifestyle during pH monitoring. In 2003, the Bravo capsule (Medtronic, Minneapolis, Minn., USA) was introduced to overcome the inconveniencies of traditional pH monitoring. With this system a radiotelemetry pH capsule is attached to the mucosal wall of the oesophagus. It simultaneously measures pH and transmits data to a pager-sized receiver clipped onto the patients' belt, thereby circumventing the need for a nasally placed oesophageal catheter. Moreover, with the capsule, data recording during 48 h (or even longer) is possible.

We review the technical aspects of Bravo wireless pH monitoring, as well as the available studies on its tolerance and diagnostic value compared to traditional pH monitoring and combined multichannel intraluminal impedance (MII) and pH monitoring (MII pH monitoring).

Fig. 1. **a** The Bravo capsule which is $6 \times 5.5 \times 25$ mm has an antimony pH electrode and reference electrode located on its distal tip. It further contains an internal battery, a transmitter and a well. **b** Delivery system designed to place and attach the capsule in the oesophagus. It can be placed transnasal or transoral. **c** The receiver collects data emitted by the capsule by radiofrequency telemetry.

Placement and Positioning of the Bravo Capsule

The Bravo capsule measures $25 \times 6 \times 5.5$ mm and has both an antimony pH and a reference electrode located on its distal tip. It further contains an internal battery, a transmitter and a mechanism to fix the capsule (fig. 1a).

After activation and calibration by submersion in pH buffer solutions of pH 7.0 and pH 1.68, the capsule is placed with a delivery system through the nose or mouth in the oesophagus (fig. 1b). The distal end of the capsule is placed 6 cm above the squamocolumnar junction (SCJ) (see below), determined during a previously performed gastroduodenoscopy. Next, a vacuum pump is connected to the delivery system which results in suction of the oesophageal wall into a well located in the upper part of the capsule. Negative pressure is maintained during 30–60 s, before an activation button activates a spring-loaded, stainless steel pin to be driven through the well of the pH capsule that attaches the pH capsule to the oesophageal wall. pH is recorded every 6 s, and data are sent every 12 s to the external receiver by radiofrequency telemetry (fig. 1c). As for traditional pH monitoring, the recorder (provided of event markers for heartburn, chest pain and other symptoms) is attached to the belt of the patient. Bravo pH monitoring is more expensive than traditional pH monitoring or combined MII pH monitoring, due to a single-use capsule rather than a reusable catheter-based pH probe. In Switzerland for example, the price of the single-use capsule and delivery system is EUR 245.

Contraindications for the use of the Bravo capsule are hemorrhagic diathesis, oesophageal varices, severe oesophagitis, oesophageal strictures or diverticle, patients with a pacemaker or defibrillator and pregnancy. If magnetic resonance imaging is necessary within 1 month after placement of the Bravo capsule, an X-ray study is necessary to be sure that the capsule has been expelled.

Traditional pH monitoring is performed 5 cm above the upper margin of the lower oesophageal sphincter (LES). This convention of position was selected to ensure that the electrode 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 oesophageal mucosal most adversely affected by gastro-oesophageal reflux [1]. Since the SCJ is located 1–1.5 cm below the LES [2], it has been proposed to place the Bravo capsule 6 cm above the SCJ, localised during a previous oesophago-gastroduodenoscopy [3]. The correctness of this approach has nicely been shown by Pandolfino et al. [4]. During endoscopy in healthy volunteers, the SCJ was localised, its distance to the incisors was noted and a stainless steel clip was fixed at this level. Then, the position of the LES was determined by manometry. The following day, a Bravo capsule was placed 6 cm above the SCJ and a traditional pH catheter was placed 5 cm above the proximal margin of the LES. Subsequently, the position of both electrodes was compared by fluoroscopy. Results showed that there was no difference in mean distance between the SCJ and either

pH electrode, or between the proximal margin of the LES and either pH electrode. Moreover inter-subject variability for the position of the capsule was smaller than the inter-subject variability for the position of the catheter tip.

Feasibility and Tolerability of Wireless Capsule pH Monitoring

A major inconvenience of traditional pH monitoring is its limited tolerability, due to the presence of a naso-oesophageal catheter during monitoring. Wireless pH monitoring is supposed to improve the comfort of the patient during the test by avoiding the need of a naso-oesophageal catheter. Several studies have reported on the tolerability of wireless pH monitoring.

In a well-designed study, Wong et al. [5] directly compared wireless capsule to traditional pH monitoring in a randomised trial including 50 patients referred for pH monitoring. The Bravo capsule was placed transnasally or, when this failed, transorally. Patients were instructed to report their symptoms, activities, diet, habits, sleep, adverse events, and lifestyle changes during the pH test, as well as overall experience of the test. Adverse effects were significantly less frequent during wireless capsule pH monitoring as compared to traditional pH monitoring, except for chest discomfort, which was significantly more frequent. Interference with daily activities, eating and sleep was significantly less during capsule pH monitoring as compared to traditional pH monitoring. Patients in the wireless pH capsule group were significantly less bothered by the test and rated their overall satisfaction higher than those randomised to traditional pH monitoring. Four domains of the SF-36 questionnaire (physical functioning, role limitation because of physical problems, social functioning and role limitation because of emotional problems) were significantly better in patients with the wireless capsule compared to traditional pH monitoring [5]. Several other studies have shown that wireless pH monitoring is well tolerated and interferes less with diet, activity, daily routine and sleep compared to traditional pH monitoring [3, 6, 7].

Chest pain has been constantly observed with the Bravo system. Overall, it has been reported in 10.5–65% of patients [3, 5, 8–10]. Chest pain ranged from a sensation of foreign body, to severe chest pain requiring the ablation of the capsule immediately after [3], or exceptionally during the test [9, 11]. The capsule can be removed using a cold snare placed loosely around the attachment base of

the capsule on the oesophageal wall, followed by gentle traction. If not successful, the snare can be closed [12, 13].

In order to elucidate the pathogenesis of chest pain induced by the Bravo capsule, Tharavej et al. [10] compared manometry readings obtained before or after placement of a Bravo capsule. Chest pain was also recorded. They found that mean distal oesophageal contraction amplitudes were significantly higher in patients with the Bravo capsule in place as compared to those patients who had no capsule in the oesophagus. Moreover, 33% of patients in the study group had distal oesophageal contraction amplitudes exceeding the 95th percentile of normal, as compared with 10% in the control group. All 6 patients with hypertensive contractions reported new-onset chest pain, while only 4 of 14 patients reported chest pain in the absence of hypertensive contractions. From these data, the authors concluded that the Bravo capsule induces contraction abnormalities like oesophageal spasms, known to be associated with chest pain.

A case of oesophageal perforation occurred during placement of the Bravo capsule, associated with the delivery system [14].

The recording efficacy of wireless pH monitoring over 48 h has been reported in several studies now. Overall, sufficient hours of pH recording to be diagnostic are obtained in more than 95% of the performed examinations [6, 7]. The most frequent reason of monitoring failure is premature capsule detachment, followed by prolonged periods of no data recording.

Bravo pH Monitoring Is Accurate to Detect GERD

The question whether wireless capsule monitoring is accurate to detect GERD has now been addressed in several studies. Moreover, studies directly comparing wireless and traditional pH monitoring have been performed.

In 2003, Pandolfino et al. [3] published the first full paper on wireless capsule pH monitoring. 41 patients with GERD symptoms (25 with confirmed oesophagitis and 16 with normal upper endoscopy) and 44 asymptomatic controls underwent ambulatory wireless capsule pH monitoring during 48 h. Sensitivity and specificity to diagnose pathologic reflux over 48 h with the wireless capsule (median total time of pH <4) were comparable to those reported in studies on traditional pH monitoring [15–17]. Although data from the first and second day were comparable for each group, 12 out of 37 GERD pa-

tients as well as 7 out of 39 asymptomatic controls had pathologic reflux (defined as more than 5.3% of total time of pH <4, which was the 95th percentile in the asymptomatic controls over 48 h) on one but not the other day of recording, an observation also reported by others [6, 18]. In view of these observations, the authors next analysed pH data from the worst day only. By doing so, sensitivity to diagnose pathologic reflux in GERD patients with endoscopically proven oesophagitis enhanced from 78 to 100% with some loss in specificity however (decrease from 95 to 85%). These data have, however, to be interpreted with caution since diagnosis of pathologic reflux for the worst day was based on a cut-off from the asymptomatic group over 48 h but not from the worst day, which would have been higher.

It has been suggested that wireless pH monitoring performed at 1 cm instead of 6 cm above the SCJ could enhance sensitivity and specificity of wireless capsule pH monitoring compared to traditional pH monitoring [19]. However, a recent study by Bansal et al. [20] has shown that wireless pH monitoring performed at 1 cm above the SCJ does not improve the sensitivity or specificity of wireless pH monitoring compared to monitoring performed at 6 cm above the SCJ.

In another study, des Varannes et al. [21] performed wireless capsule pH monitoring during 48 h and traditional pH monitoring (during the first 24 h) in parallel in 40 patients with GERD. Surprisingly, the total time of pH <4 as well as the total number of reflux events reported by capsule pH monitoring were significantly lower as compared to traditional pH monitoring. Despite this, there was a strong and highly significant correlation between the 24-hour oesophageal acid exposure recorded by both recording systems. An 88% concordance between both recording systems to diagnose GERD was found when the cut-off of total time of pH <4 for capsule pH monitoring calculated from the regression equation was used. Moreover, sensitivity to establish a relation between symptoms and reflux was comparable for both. Although these data show that wireless capsule pH monitoring is a good tool to diagnose GERD, they suggest that the system is less sensitive compared to traditional pH monitoring. However, in a similar study with healthy volunteers, Pandolfino et al. [4] were able to show that the difference in pH recording was due to an overestimation of acidity by traditional pH monitoring, due to a flaw in the software algorithm. Indeed, although they confirmed the observations from des Varannes et al. [21] that total time of pH <4 was significantly inferior with wireless capsule pH monitoring compared to traditional pH monitoring, they

could elegantly show by using consumption of orange juice during pH monitoring as an internal control, that the pH recorded by the capsule was closer to that of the known pH of orange juice than did traditional pH monitoring. After manual correction for the error between the recorded and real pH for all data of the pH tracing, the apparent discrepancy in acid exposure time reported by the two systems disappeared. However, the number of reflux episodes reported by traditional pH monitoring remained significantly higher compared to the number reported by wireless capsule pH monitoring [22]. Pandolfino et al. [22] were able to show that this discrepancy was mainly due to differences in detection of short, but not long reflux events. Moreover, short reflux events accounted for only a minority of total acid exposition. They thus concluded that the enhanced number of reflux events reported by traditional pH monitoring had only minor clinical significance, if any – a conclusion also made by des Varannes et al. [21]. The difference in short reflux events may partly be due to the lower sampling frequency of wireless pH monitoring compared to traditional pH monitoring (every sixth and fourth second, respectively).

From these studies it is clear that the values used to define pathologic reflux in traditional pH monitoring may not be transposed to wireless capsule pH monitoring. Although Pandolfino et al. [3] determined 5.3% of total time of pH <4 as upper limit of normal (95th percentile), the group of healthy volunteers was poorly defined. The question of the upper limit of physiologic acid reflux, defined as the 95th percentile in asymptomatic controls, has been best answered in a study by Wenner et al. [7]. In this study, wireless capsule pH monitoring was performed in 50 asymptomatic volunteers, 25 men and 25 women evenly distributed within each gender, with a minimum of 2 subjects in each 5-year age interval. In this study, the 95th percentile of percentage of total time of pH <4 over 48 h was 4.4%. The 95th percentile of percentage of pH <4 in upright position was 6.3%, 3.7% for supine position and 9.6% postprandial. The 95th percentile for the number of reflux episodes over 48 h was 93 and for those lasting for more than 5 min this number was 5.

Discussion

Since the introduction of wireless capsule pH monitoring in 2003, several studies have clearly shown its feasibility and technical reliability in the diagnosis of GERD.

Moreover, wireless capsule pH monitoring is better tolerated and interferes less with diet, activity, daily routine and sleep as compared to traditional pH monitoring. The main inconveniency of wireless capsule pH monitoring, however, is induction of thoracic discomfort (which can vary from mild foreign body sensation to severe chest pain) induced by the capsule attached to the oesophageal wall, and reported in 10–65% of the patients. It has been proposed that chest pain is related to disturbances in oesophageal motility, induced by the capsule [10]. Whether these motility disturbances influence the oesophageal pH is, however, not known.

Despite enhanced tolerance and recorded time, the expectation that this would improve sensitivity and specificity of wireless pH monitoring compared to traditional pH monitoring has not been achieved. It also remains to be proven whether using data from the worst day only enhances accuracy of wireless pH monitoring compared to traditional pH monitoring.

From the studies [4, 21] that performed traditional and wireless pH monitoring in parallel, it is also clear that data obtained with both recording systems cannot be compared to each other. Therefore, new reference values above which acid reflux is considered as pathologic are necessary for wireless pH monitoring. Based on available data, a cut-off at 4.4% of total time of pH <4 over 48 h

(which was the 95th percentile of percentage of total time of pH <4 over 48 h in a study on 50 healthy volunteers, well balanced for age and sex [7]) offers at present the best basis for the routine use of wireless pH monitoring in the diagnosis of patients with GERD.

Finally, wireless pH monitoring will probably be challenged by combined MII pH monitoring in the future. This latter has the advantage to detect acid as well as weakly or non-acid reflux and enables exact assessment of the proximal extent of refluxed material [23]. For patients on acid-suppressive therapy, where isolated pH monitoring has a very low diagnostic yield, combined MII pH monitoring may show in a proportion of patients an association between symptoms of regurgitation, cough, chest pain or heartburn and non-acid reflux [24]. Wireless pH monitoring is therefore mainly useful in patients off acid-suppressive therapy to diagnose whether or not acid reflux accounts for patients symptoms. However, in this population, studies are warranted to compare sensitivity and specificity of wireless pH monitoring compared to combined MII pH monitoring. Indeed, Hila et al. [25] have recently shown that additional information of impedance on pH data eliminates false-positive interpretation of acid reflux into the oesophagus, thereby enhancing the specificity of pH monitoring compared to pH monitoring alone.

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