Turk J Gastroenterol *2017; 28(Suppl 1): S16-S21*

Indications of 24-h esophageal pH monitoring, capsule pH monitoring, combined pH monitoring with multichannel impedance, esophageal manometry, radiology and scintigraphy in gastroesophageal reflux disease?

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Cite this article as: Vardar R, Keskin M. Indications of 24-h esophageal pH monitoring, capsule pH monitoring, combined pH monitoring with multichannel impedance, esophageal manometry, radiology and scintigraphy in gastroesophageal reflux disease? Turk J Gastroenterol 2017;28(Suppl 1); S16-S21

ABSTRACT

Ambulatory esophageal pH monitoring is an essential method in patients exhibiting signs of non-erosive reflux disease (NERD) to make an objective diagnosis. Intra-esophageal pH monitoring is important in patients who are non-responsive to medications and in those with extraesophageal symptoms, particularly in NERD, before surgical interventions. With the help of the wireless capsule pH monitoring, measurements can be made under more physiological conditions as well as longer recordings can be performed because the investigation can be better tolerated by patients. Ambulatory esophageal pH monitoring can be detected within normal limits in 17%-31.4% of the patients with endoscopic esophagitis; therefore, normal pH monitoring cannot exclude the diagnosis of gastroesophageal reflux disease (GERD). Multi-channel intraluminal impedance pH (MII-pH) technology have been developed and currently the most sensitive tool to evaluate patients with both typical and atypical reflux symptoms. The sensitivity of a pH catheter test is 58% for the detection of acid reflux compared with MII-pH monitoring; further, its sensitivity is 28% for the detection of weak acid reflux compared with MII-pH monitoring. By adding impedance to pH catheter in patients with reflux symptoms, particularly in those receiving PPIs, it has been demonstrated that higher rates of diagnoses and symptom analyses can be obtained than those using only pH catheter. Esophageal manometry is used in the evaluation of patients with functional dysphagia and unexplained noncardiac chest pain and prior to antireflux surgery. The use of esophageal manometry is suitable for the detection of esophageal motor patterns and extreme motor abnormalities (e.g., achalasia and extreme hypomotility). Esophageal manometry and ambulatory pH monitoring are often used in assessments prior to laparoscopic antireflux surgery and in patients with reflux symptoms refractory to medical treatment. Although the esophageal motility is predominantly normal in patients with non-acid reflux, ineffective esophageal motility is often monitored in patients with acid reflux. In the literature, there are contradictory and an insufficient number of studies regarding radiological methods for the diagnosis of GERD. There are inconsistent values for sensitivity and specificity among the barium studies. There are inadequate studies in the literature involving scintigraphic examinations in the diagnosis of GERD, and a majority of existing studies have been conducted in the pediatric group. The results of a few studies do not provide sufficient contribution toward the implementation in clinical practice.

Keywords: GERD diagnosis, esophageal pH monitoring, esophageal impedance monitoring, esophageal manometry, esophageal scintigraphy

TWENTY-FOUR-HOUR INTRA-ESOPHAGEAL pH MONITORING, CAPSULE pH MONITORING

Although symptoms are evident in two-third of the patients with GERD, there is no objective finding in upper gastrointestinal endoscopy for the diagnosis of GERD. Cases in this group are referred to as NERD. Intra-esophageal ambulatory pH monitoring is needed to obtain objective data for the diagnosis of NERD. This is an important test in patients who are non-responsive to medication and have extraesophageal symptoms, particularly in NERD before an operation. Esophageal pH monitoring was developed in the 1960s and entered clinical use in the 1970s. The ad-

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dition of reflux-symptom association to this method, which is an important feature, was realized in the 1980s (1). The use of ambulatory 24-h esophageal pH monitoring has facilitated a better understanding of GERD. A practical approach toward the details of gastroesophageal and laryngopharyngeal reflux and to clinical symptoms associated with reflux episodes could be achieved. To avoid discomfort encountered during examinations related with catheter, the use of a catheter-free radio telemetry Bravo pH capsule (Medtronic, Inc., Minneapolis, MN) is becoming popular. It has been used in adult patients since 2004 and in pediatric patients since 2006 (2,3). With the help of this system, measurements can be made under more physiological conditions as well as the investigation can be better tolerated by patients (4). Because the measurement can be made until the Bravo capsule falls (which can take up to 5 days in some cases), it allows intra-esophageal pH monitoring lasting longer than 24 h. Bravo capsule monitoring is done for 48 h as a standard. The attachment failure possibility of the Bravo capsule to the esophageal wall has been reported as 2%-12% (5,6). Generally the attachment of Bravo capsule at 6 cm proximal to the squamocolumnar junction determined through an endoscopic examination is preferred (7). In catheter pH monitoring, the catheter is placed at 5 cm proximal to the LES detected by manometric evaluation. As it has been shown that it is difficult to attach a capsule to the columnar epithelium, a catheter system is recommended to be used in patients with Barrett's esophagus (8). A capsule pH monitoring which is better tolerated and longer monitoring can be undertaken was developed to increase diagnostic sensitivity. Measurement differences may occur in catheter and capsule pH monitoring as the pH recording intervals are different (although the record is taken once in every 4 seconds in the catheter method, it is taken every 6 seconds in the capsule method). Although the capsule is fixed at the level of LES in the capsule pH monitoring, the catheter tip can move to the stomach when swallowing; as the capsule pH monitoring takes shorter records, it captures fewer reflux episodes than conventional methods (9-11). Technical failure rate of the capsule pH monitoring is 4.1%-5% (12-14). Because the catheter pH monitoring can cause discomfort in patients, it may lead them to eat less and behave differently in their daily lives during the monitoring process (15,16). Esophageal pH monitoring can be normally identified in 17%-31.4% patients with endoscopic esophagitis (10,17-21). Therefore, a normal pH monitoring cannot be excluded in the diagnosis of GERD.

Although normal value of total time period of pH less than 4 is 4.2% for catheter pH monitoring is, while it is 4.4%-5.3% for the capsule pH monitoring (48 h) (4,11,22). In a prospective study comparing the catheter and capsule pH monitoring, there was no significant difference between them when used for the diagnosis of GERD; longer reflux durations were identified in the capsule pH monitoring than in the catheter pH monitoring (23). In the study by Hakanson et al. (24) in which both capsule and catheter pH monitoring were simultaneously used, esophageal acid exposure time detected in capsule pH monitoring technique was approximately half of the value that was found with catheter technique ($p<0.05$). The pH data obtained with both techniques in this study were correlated. The 48-h capsule pH monitoring is applicable, but it continuously identifies lower esophageal acid exposure than the technique with catheter. Therefore, these two methods could not be used interchangeably in clinical practice. If the reflux-symptom association probability (SAP) is ≥95% and/or symptom index (SI) is ≥50%, the SAP can be considered to be positive even in the prolonged use of capsule pH monitoring, same as that in the catheter pH monitoring (1,25). The catheter pH monitoring is the best method in GERD diagnosis because of its 79%-96% sensitivity, 85%-100% specificity, and 98% accuracy (13,15,26-30). Based on the pathological acid exposure and positive SAP values in the prolonged use of pH monitorizations, while the diagnosis of GERD is 61% (according to the cumulative average), it is 76% with the worst day analysis. The prolonged use of capsule pH monitoring increases the test sensitivity and diagnostic rate in patients with negative catheter pH monitoring test results and in patients with continuing esophageal symptoms (31). Pandolfino et al. (5) reported 78.3%-100% sensitivity and 84.5%-94.8% specificity for this method. The rate of real GERD diagnosis is 39.4% in capsule pH monitoring examinations and 36.4% in catheter pH monitoring examinations (32). Nasi et al. (33) detected the prevalence of typical symptoms as 49.7% and the prevalence of atypical and/or extraesophageal symptoms as 50.3% in patients who admitted for a catheter pH monitoring. Catheter pH monitoring, when performed with a dual probe (distal and proximal esophagus), is superior to pH monitoring with single sensor capsules in patients whose main symptoms are extraesophageal or globus (23). According to Hirano et al. (34), a capsule pH monitoring has the highest sensitivity in GERD monitoring compared with conventional methods (bile, pH monitoring, and MII-pH) and it is also the best tolerated method.

COMBINED pH MONITORING and MULTICHANNEL IMPEDANCE

Impedance is the measurement of resistance to electric current in alternating current circuits. The data obtained in esophageal impedance examinations vary depending on the luminal content, mucosa, and wall thickness. Electrical impedance is the opposite of conductivity. If there is non-conductive content in the medium (e.g., air), no current is formed between the two metal rings, resulting in high impedance values. If the luminal content is liquid, the impedance drops because of increased conductivity (35). Depending on the changes in the mucosa, basal impedance becomes abnormally low in patients with esophagitis or Barrett's esophagus. Multi-channel impedance catheters have been developed to understand whether the content that we detect in the esophageal lumen via a single channel moves from proximal to distal (swallow) or from distal to proximal (reflux) (36,37). Because the measurement is taken between two metal rings, distal reflux episodes are analyzed through the channels at 3rd, 5th, 7th, and 9th cm and proximal reflux episodes are analyzed through the channels at 15th and 17th cm. The pH sensor located on the impedance catheter at 5 cm proximal to the LES yields information about the acidic contents in the lumen. The term "weak acid reflux", which was noticed after understanding the nature (air-water), direction (swallowing-reflux), and pH (acid, weak acid, or weak alkaline=non-acid reflux) of the content in the esophagus through MII-pH monitoring, was started to be used in GERD (38-40). MII-pH monitoring is the most sensitive tool to evaluate GERD in patients with both typical and

atypical reflux symptoms (41-46). The impact of the method on symptom association has clearly been demonstrated in several studies (47-49). As fluid and gas reflux episodes can be detected through MII-pH monitoring, non-acid reflux episodes that cannot be comprehensively determined using other techniques can also be detected (37,50). For GERD, the sensitivity in MII-pH monitoring technique is 74%. MII-pH test monitoring is an important examination both in the diagnosis of GERD and in the assessment of the severity of disease and treatment response (51). Since this technique is multi-channeled, proximal reflux episodes 15 cm above the LES can also be detected. The role of weak acid reflux can effectively be assessed through MII-pH monitoring (47,52-56). Although only the MII-pH monitoring and pH monitoring tests were compared, with the addition of PPI response, a decrease in the detection of reflux and an increase in functional heartburn cases were determined (57). The sensitivity of the catheter pH monitoring for the detection of acid reflux is 58% compared with MII-pH and 28% for the detection of weak acid reflux compared with MII-pH monitoring. Eighty-three percent of the weak acid reflux episodes detected through MII-pH cannot be determined by using a catheter pH monitoring. A pH monitoring alone is very sensitive in detecting acid reflux, but has a low specificity compared with combined MII-pH. It may lead to an incorrect diagnosis in 22% cases with regard to abnormal acid reflux (58). In patients with abnormal weak acid or non-acid reflux under treatment, a positive predictive value of MII-pH is more probable (93%) in terms of basal acid reflux. The detection of abnormal impedance findings in patients receiving treatment can be the predictor of acid reflux that emerges when the treatment is ceased. MII-pH monitoring in patients with refractory reflux can be the best diagnostic option in the evaluation of reflux symptoms (59). Mainie et al. (60) detected non-acid reflux in at least 37% patients in MII-pH examinations that they carried out in patients with persistent symptoms, despite their use of at least double the dose of PPI. With the addition of impedance to a pH meter, it has been demonstrated that a higher rate of diagnoses and symptom analyses can be obtained in patients with reflux symptoms, particularly in those receiving PPI (49).

ESOPHAGEAL MANOMETRY

Esophageal manometry that enables neuromuscular activity and contraction characteristics of the esophagus to be understood is used in the evaluation of functional dysphagia, unexplained noncardiac chest pain, and in the evaluation of patients prior to antireflux surgery. The "station pull-through" technique discovered in 1956 (49) is still widely used in classical esophageal manometric examination. With this technique, the LES can be determined by the detection of a high-pressure zone observed during the withdrawal of the catheter lowered into the stomach. Some of the negative aspects of this technique are experiencing difficulties in tolerability, longer duration of the process, and limitations in the assessment of LES movements or relaxation. In 1976, Dent resolved this problem using a "sleeve sensor" (61). Instead of measuring the LES pressure and relaxation from a single point, Dent's sleeve method provides the possibility to make a longer measurement, for example, 6 cm. Thus, artifacts caused by the movements of the diaphragm are reduced to a minimum. High-resolution manometry (HRM) has been used in the analysis and understanding of esophageal motility since the 1980s (62-64). The use of esophageal manometry is suitable for the detection of esophageal motor patterns and extreme motor abnormalities (e.g., achalasia and extreme hypomotility) (65,66). Esophageal manometry and ambulatory pH monitoring are frequently used in the evaluation before antireflux surgery and in patients who have reflux symptoms and are refractory to medical treatment (67,68). According to the retrospective studies of Chan et al. (69) in which HRM and pH monitoring assessments were made before laparoscopic antireflux surgery, there is no GERD evidence in 23.9% cases. Although spastic disorders are more frequent in those without GERD (43.9% in patients with non-GERD, 23.1% in patients with GERD, $p<0.001$), hypomotility and normal patterns are more common in those with GERD. In preoperative examinations performed before the standard 360° fundoplication (Nissen), an absolute or relative contraindication was found in 1 out of 14 patients. Normal motility was detected in 86% patients with non-acid reflux; 71%, patients with acid reflux; and 60%, non-reflux patients. There is insufficient esophageal motility in 24% patients with acid reflux and 5% patients with non-acid reflux ($p=0.11$). Although the esophageal motility is predominantly normal in patients with non-acid reflux, ineffective esophageal motility is often observed in patients with acid reflux (70).

RADIOLOGY

In the literature, there are limited and contradictory data regarding radiological methods for the diagnosis of GERD. The diagnostic methods in current studies are unsatisfactory to be implemented in clinical practice. Neumann et al. (71) made fluoroscopic examinations with barium in their prospective study of 51 patients, and they found the sensitivity of the test as 43% and specificity as 51% by comparing the results with esophageal manometric examination; as a result, they made the interpretation that the role of fluoroscopy is limited in the morphological assessment of gastroesophageal junction. The sensitivity of the method, which is called the Water Siphon Test (WST) wherein barium studies are compared with pH monitoring for the diagnosis of GERD, was found as 74% and the specificity as 71%; barium studies are useful in screening the patients in the presence of clinical GERD symptoms. In addition, the sensitivity of barium studies has been identified as the highest when maneuvering is used to reveal reflux (72). In another similar WST study, the sensitivity of the method has been reported as 71% and the specificity as 31% (73). In their prospective studies that were pH monitoring comparative and were conducted with barium radiography, Aksglaede et al. (74) detected the sensitivity of the method as 52% and the specificity as 100%.

SCINTIGRAPHY

There are inadequate studies in the literature regarding scintigraphic examinations in the diagnosis of GERD and the majority of existing studies were conducted in the pediatric group. The results of a few studies do not provide sufficient contribution to their implementation in clinical practice. In a study prospectively conducted in 30 patients, it was stated that gastroesophageal reflux was scintigraphically demonstrated in 27 (90%) out of 30

patients (75). The sensitivity was found as 100% and the specificity as 51% in another study in which the scintigraphic method was compared with endoscopy in 12 patients. Because of low specificity (33%-57%), it has been interpreted as a test with low accuracy level that cannot be accepted as a screening test (76). Hsu et al. (77) studied a comparison of single-photon emission computed tomography (SPECT) and endoscopy in 60 patients for the diagnosis of esophagitis and found the sensitivity of the method as 95.2% and the specificity as 72.2%; they have pointed out that SPECT has high sensitivity and accuracy in the detection of esophagitis in patients with GERD.

RECOMMENDATIONS

pH Monitoring /Impedance

- The use of 24-h multichannel intra-esophageal impedance pH monitoring (24-h MII-pH) or pH monitoring is appropriate for patients who are refractory to treatment and in patients who cannot be diagnosed with GERD after an endoscopic examination. (Level of evidence: 1B)
- In particular, 24-h MII-pH monitoring is superior to 24-h intra-esophageal pH monitoring in patients who are tested under PPI. (Level of evidence: 1C)
- Long period wireless capsule pH monitoring increases the sensitivity and rate of diagnosis in patients whose 24-h intra-esophageal pH monitoring is found negative but reflux symptoms continue or in patients who cannot be diagnosed by using pH monitoring. (Level of evidence: 3B)

Manometry

- Esophageal manometric examination should be done in PPI refractory patients to make a differential diagnosis. (Level of evidence: 3B;)
- Esophageal manometric examination should be done to investigate the presence of esophageal motility defects before reflux surgery. (Level of evidence: 3B;)
- Esophageal manometric examination should be used to detect the lower esophageal sphincter necessary for the determination of the location of MII-pH and catheter pH monitoring. (Level of evidence: 5)

Radiology

- Radiological examination is not a reliable method for the diagnosis of reflux. (Level of evidence: 5)

Scintigraphy

- In the literature, there is insufficient evidence regarding whether or not scintigraphy is appropriate for the diagnosis of gastroesophageal reflux in adults and its use is not recommended. (Level of evidence: 5)

Conflict of Interest: No conflict of interest was declared by the authors.

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