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Review Article

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Esophageal pH and Combined Impedance-pH Monitoring in Children

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Esophageal pH monitoring is considered the gold standard for the diagnosis of gastroesophageal reflux disease because of the normal ranges across the pediatric age range. However, this method can only detect acid reflux. Multichannel intraluminal impedance-pH (MII-pH) monitoring has recently been used for the detection of bolus reflux in infants and children. This method allows for the detection of liquid, gas or mixed reflux in addition to acid, weakly acidic or weakly alkaline reflux. MII-pH monitoring can record the direction of flow and the height of reflux, which are useful parameters to identify an association between symptoms and reflux. However, the technique is limited by its high cost and the lack of normative data of MII-pH in the pediatric population. Despite certain limitations, MII-pH monitoring will become more common and gradually replace pH monitoring in the future, because pH monitoring is part of MII-pH.

Key Words: Esophageal pH monitoring, Impedance-pH monitoring, Gastroesophageal reflux, Infant, Child

INTRODUCTION

Gastroesophageal reflux (GER) is the passage of gastric contents into the esophagus with or without vomiting and regurgitation, and it is common among infants and children [1]. Gastroesophageal reflux disease (GERD) is diagnosed when GER causes troublesome symptoms and/or complications [1,2]. Although various tests have been developed for the diagnosis of GERD, it is difficult to accurately diagnose GERD and to determine a causal association between symptoms and reflux.

Esophageal pH monitoring was initially introduced in 1969. It has been deemed the gold standard for the diagnosis of GERD since the 1980s [3]. It is useful because the upper limit of normal for esophageal acid exposure (% time pH $<$4) is defined across the age spectrum [4]. However, this technique is limited because it can only detect acid reflux in the esophagus. Multichannel intraluminal impedance (MII) was firstly reported in 1991. It was developed to evaluate the movement of fluid, solid, and air in the esophagus regardless of its pH [5]. Combined multichannel intraluminal impedance-pH (MII-pH)

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monitoring has been used for the detection of reflux in children since 2002 [6-8].

ESOPHAGEAL pH MONITORING

Twenty-four-hour esophageal pH monitoring measures the frequency and duration of acid reflux episodes. The main advantage of this test is its ability to quantify acid reflux and evaluate the correlation of symptoms with acid reflux. The definition of normative values for esophageal acid exposure time could help in interpreting the results of this test; however, the cutoff value for pathological GER remains the subject of debate [9].

Originally, the most popular pH sensors were glass electrodes. Antimony electrodes have become more popular in recent years, although they are less accurate than glass electrodes in addition to hygiene issues and their high cost. Ion-sensitive field effect (ISFET) pH electrodes are modified field-effect transistors [10]. However, their ends are stiff and they are difficult to insert in infants and children. Antimony electrodes have the slowest response times. Total acid exposure time is not substantially altered by a slow electrode response time; however, the accuracy of the symptom association with reflux episodes may be affected [1,2,10].

In fact, pH monitoring is often performed despite its major limitations because of the inability to detect nonacid reflux (pH above 4), and especially in infants who are often fed milk-based formulas or breast milk. Furthermore, this test is not accurate for the detection of reflux episodes in patients undergoing acid suppressive treatment. In addition, pH monitoring is limited for distinguishing between patients in whom symptoms are related to nonacid reflux episodes and those in whom symptoms are related to no type of reflux [11]. Another drawback is that the test cannot detect superimposed acid reflux episodes (i.e., acid reflux occurring while the acid of a previous reflux episode is still being cleared). Lastly, the results are affected by the ingestion of acidic foods and drinks [12].

MULTICHANNEL INTRALUMINAL IMPEDANCE–pH MONITORING

MII-pH monitoring provides a comprehensive characterization of reflux episodes that includes chemical properties (i.e., acid, weakly acidic or weakly alkaline), physical properties (i.e., liquid, mixed, gas), height of the reflux, acid clearance and bolus clearance [11]. Table 1 shows the differences between pH and MII-pH monitoring.

Impedance monitoring measures changes in electrical impedance between each electrode assembled on an esophageal probe. The test is based on the principle that impedance is inversely correlated to the ionic concentration of luminal substances [12]. A bolus containing high ionic substances (e.g., saline, refluxate) results in low impedance measurements and a bolus with low ionic substances (e.g., air) results in high impedance. The velocity and direction of a bolus can be calculated by measuring the time and distance of impedance changes. The height of the bolus can also be evaluated [8,10].

The main advantage of combined MII-pH monitoring is that it can detect all reflux episodes because MII can record the direction of esophageal flow and the pH sensor enables the classification into acid, weakly acidic, and weakly alkaline reflux. Another advantage of this method is that it can determine the correlation between symptoms and types of reflux

Table 1. Comparison between pH Monitoring and Multichannel Intraluminal Impedance-pH Monitoring

	pH monitoring	MII-pH monitoring
Acid reflux	Yes	Yes
Superimposed acid reflux	Undetectable	Yes
Nonacid reflux	Undetectable	Yes
Gas reflux	Undetectable	Yes
Direction	Undetectable	Yes
Height of reflux	Undetectable	Yes
Bolus clearance	Undetectable	Yes
Chemical clearance	Yes	Yes
Postprandial reflux	Undetectable	Yes
Cost	Cheap	Expensive
Interpretation	Easy	Difficult

MII: multichannel intraluminal impedance.

episodes. It can also evaluate symptoms associated with reflux in the presence of acid suppression. Therefore, the negative results of MII-pH monitoring are of value to exclude reflux as a significant factor associated with symptoms compared with pH monitoring [11].

MII-pH has certain limitations. As a result of ethical issues, normal values have not been established for the pediatric age range. The costs of this procedure are approximately 4-fold higher than those of pH monitoring, and the analysis requires approximately 30 minutes to 4 hours depending on the experience of the examiner and the frequency of reflux [12].

SIGNIFICANCE OF NONACID REFLUX

The proportion of nonacid reflux episodes relative to the total number varies from 45% to 90% in infants and children [7,13-16]. Nonacid reflux is especially prevalent in infants because of pH buffering associated with frequent milk intake.

Recent data proposing an association between atypical (i.e., extraesophageal) symptoms and nonacid reflux suggest that nonacid reflux could be significant in infants and children. Wenzl et al. [13] reported that 78% of the symptom related reflux episodes were nonacid reflux in patients with breathing irregularities. Rosen and Nurko [14] reported that the correlation of symptoms with nonacid reflux episodes was stronger than that with acid reflux episodes in a study that analyzed 28 children with respiratory symptoms. Mousa et al. [15] found that nonacid reflux constituted 48% of total reflux episodes in 25 infants presenting with apnea or an apparent life-threatening event. Furthermore, 15.2% of all apnea episodes were associated with a reflux episode; 8.2% were associated with nonacid reflux and 7.0% with acid reflux. Magistà et al. [16] reported that nonacid reflux represented 76% of all reflux episodes in preterm infants with apnea. Impedance monitoring increased the probability of a positive symptom association by 22% in 50 infants and children with various atypical symptoms [17].

INDICATIONS

In 1995, the indications for pediatric esophageal pH monitoring were established by the North American Society for Pediatric Gastroenterology and Nutrition. These included the evaluation of atypical symptoms possibly caused by GERD, assessment of the effectiveness of therapy including medication dosage and surgery, patients with unexplained recurrent pneumonia and patients prior to fundoplication [18].

The indications for combined MII-pH monitoring are similar to those described for pH monitoring: to quantify reflux in patients with mostly atypical symptoms, to measure reflux in patients who do not show improvement in response to antireflux medication, and for research purposes [8]. This technique can also be useful for patients off or on proton pump inhibitors and those receiving either bolus-based or continuous enteral feeding because of its ability to detect nonacid reflux. Therefore, MII-pH can be used to assess reflux and the correlation between reflux episodes and specific discontinuous symptoms, such as cough, apnea, and other respiratory symptoms, behavioral symptoms, and to assess the efficacy of acid suppressive therapy. In addition, this method is useful to diagnose patients with aerophagia because it can detect air boluses.

PROTOCOLS

MII-pH equipment and preparation

In general, the equipment and preparation used for pH monitoring and MII-pH monitoring are similar except the probes used for each method. The combined MII-pH test requires a recording device, software, buffer solutions, probes, and other aids.

In MII-pH, 3 different age- or height-appropriate probes are used as follows: infant (height$<$75 cm), pediatric (75 cm$<$height$<$150 cm), and adult (height$>$150 cm) probes. The diameter of each MII-pH probe is 2.13 mm (6.4 Fr). It should have at least 7 impedance electrodes and 1 pH sensor (mainly antimony). The segment between each pair of electrodes is consistent with 1 impedance channel.

Probes containing 7 impedance electrodes have 6 impedance channels. In the infant probe type, the distance between individual impedance electrodes is 1.5 cm and a pH sensor is placed in the middle of the most distal impedance channel. In the pediatric and adult probes, the distance between electrodes is 2 cm and the pH sensor is placed at the center of the first or second channel from the distal impedance channel, respectively [8].

The reference electrode can either be built into the esophageal probe (internal reference) or placed outside the esophagus (external reference). Probes with an internal reference electrode are reliable and technically easy to use because an external skin electrode is not needed. However, this type of probe crosses the lower esophageal sphincter (LES) and could increase the number of reflux episodes because of the location of the internal reference electrode, which is placed at the tip of the probe [19].

Before each testing session, the pH sensor should be calibrated using 2 different pH buffer solutions. For external reference probes, the external reference electrode should be attached to the skin and both the finger and the sensor should be placed in the buffer solution simultaneously. For internal reference probes, this is not required. MII-pH probes with unstable calibrated pH sensors can cause a significant pH drift and thus should not be used.

Position of the probe

In general, MII-pH probe is passed through the nostrils into the esophagus after a fasting period of at least 3 hours. The pH sensor should not be coated with the gel used for transnasal passage because it could lead to inaccurate readings. The pH sensor should be placed at a level 2 vertebrae above the diaphragm [8]. Depending on the probe type, the pH sensor can also be fixed approximately 2 cm (infant type), 3 cm (pediatric type), or 5 cm (adult type) above the LES. Proper probe positioning should be determined by fluoroscopy during a respiratory cycle. Another method is based on the use of the Strobel formula ($0.252\times$height [cm]$+5$) [20], which calculates the length form the nares to the LES in centimeters for infants. However, this method can result in the overestimation of esophageal length with increasing height [8].

Patient instruction

The patients should follow a regular diet during the 24 hours of testing. The data collected include relevant symptoms, position (supine, upright), mealtimes (beginning, end), and other events (e.g., disconnection of the skin electrode, correction of probe position) [8]. The patients or their parents should press the ''event'' buttons on the recording device whenever each relevant symptom occurs. In addition, the parents can complete a symptom diary by recording the time on the recording device at mealtimes, position changes, and symptom occurrences.

Patients should avoid acidic foods and carbonated beverages because of their potential effect on the interpretation of data. In addition, they should abstain from very cold or very hot foods or beverages because the sensitivity of the pH sensor is influenced by temperature [21]. For testing off antireflux therapy, antireflux medications should be stopped at least 7 days before the test for proton pump inhibitors, 3 days for H2 blockers, and 2 days for prokinetics [21,22]. Because a nasogastric tube increases reflux and a pacifier causes a false positive reflux, their use should be limited [19,21].

On completion of the study, the device is turned off and the probe is removed. The examiner downloads the data to a computer and performs the analysis using the appropriate software.

Analysis

Before running the automatic data analysis, the examiners should identify and exclude potential artifacts (pseudo-reflux, or impedance/pH signal loss) and add and/or delete any events such as symptoms, meals and body position according to patient diary. Meal periods are often excluded from the analysis and each postprandial period is usually 1 or 2 hours. During the automatic data analysis, the examiner should select between the following pH options: pH measurements related to retrograde bolus movement or pH measurements at the time of pH fall below 4. The data are then re-analyzed manually to confirm, add, and/or delete reflux episodes.

In clinical practice, MII-pH monitoring is a time consuming task because of the manual data analysis. Generally, the automatic analysis has high sensitivity and rather low specificity. Because intra- and interobserver variability is relatively high, even among skilled examiners, the automatic analysis should be performed in clinical practice to decrease the time required for data analysis [23].

DEFINITIONS

The definitions of calculated and analyzed param-

Table 2. Definitions of Reflux Parameters in Multichannel Intraluminal Impedance-pH Monitoring

Parameter	Definition
Liquid MII reflux episode	Fall in impedance ≥50% from baseline in at least 2 distal channels
Acid reflux	pH<4 lasting for at least 4 s
Nonacid reflux	pH≥4
Weakly acidic reflux	4≤pH<7
Weakly alkaline reflux	pH≥7
Gas reflux	Rapid increase in impedance>3,000 Ω in at least 2 channels
pH-only acid reflux	pH fall from ≥4 to <4 lasting ≥4 sec and not associated with a MII reflux
Acid clearance time	Time required for acid clearance from the esophagus
Reflux index (RI)	The total percentage of time of esophageal exposure to pH<4
Bolus clearance time	Time required for bolus clearance from the esophagus
Bolus exposure index (BEI)	The total percentage of time that a bolus is exposed in the esophagus

MII: multichannel intraluminal impedance.

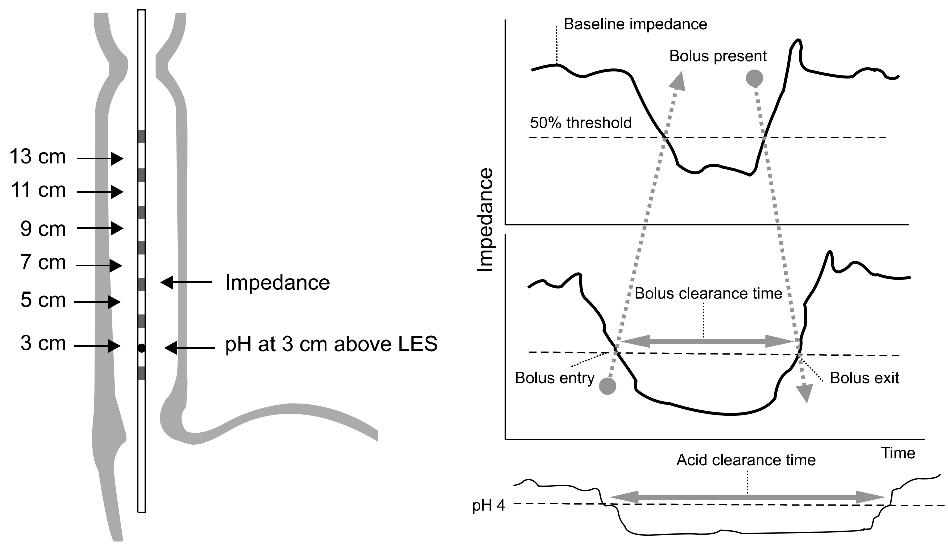

Fig. 1. Pediatric type probe and bolus acid reflux in multichannel intraluminal impedance-pH (MII-pH) monitoring. A combined MII-pH probe has 6 impedance channels and a pH sensor. The impedance electrodes are 2 cm apart from each other and the pH sensor is in the middle of the most distal impedance channel. The pH sensor is placed 3 cm above the lower esophageal sphincter (LES). The probe with the internal reference electrode crosses the LES. As the bolus reaches the impedance channel, impedance decreases rapidly. Bolus entry occurs at the 50% drop in impedance from baseline and bolus exit occurs above the 50% threshold value. Bolus reflux is defined as an impedance drop in at least 2 distal channels. Bolus clearance time is the time from bolus entry to exit. The retrograde bolus reflux is shown as bolus entry progression from distal to proximal impedance channels (dashed arrows) followed by proximal to distal bolus exit progression. Bolus reflux episodes during which the pH drops from above to below 4 are considered acid. Acid clearance time is the tie of esophageal exposure to a pH<4.

eters are shown in Table 2. Because of the impedance drop in at least 2 distal channels by definition, the minimal height of MII reflux episodes should be approximately 4 cm or 6 cm above the LES for infant or pediatric probes, respectively (Fig. 1). MII-pH classifies reflux episodes into liquid, gas, or mixed (gas-liquid, liquid-gas). MII reflux episodes can be categorized as acid, weakly acidic or weakly alkaline according to the pH change. Weakly acidic and weakly alkaline refluxes are grouped as acid reflux. Therefore, MII-pH monitoring can detect 3 main types of reflux episodes: acid MII reflux, which is detected by both impedance electrodes and the pH sensor; nonacid reflux, detected only by impedance electrodes; and pH-only episodes, which are detected only by the pH sensor and not by impedance electrodes.

In general, the duration of bolus exposure is shorter than that of acid exposure because of differences in the clearance time. The acid exposure can be calculated to one related to retrograde bolus movement (reflux-related acid exposure) and the other at the time of a pH <4 (total acid exposure) according to the pH options. The reflux-related acid exposure is considerably shorter than the total acid exposure [7,24].

INTERPRETATION

A drop in esophageal pH to a value below 4 is conventionally defined as an acid reflux episode. The selection of this cut-off value is based on the fact that the main proteolytic enzyme, pepsin, is active at a pH <4, and heartburn caused by acid perfusion generally occurs at a pH<4 in adults [1,10,11]. Several scoring systems have been developed, such as the DeMeester or Boix-Ochoa scores but the score does not include information on reflux-symptom association and no system is superior to measuring the reflux index (RI [% time pH<4]) [10, 11].

In 2001, it was recommended that the upper limit of normal for the RI is considered as up to 12% until 1 year of age and up to 6% after that [4]. In 2009, the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition reported that an RI>7% is considered abnormal, an RI<3% is considered normal, and an RI between 3% and 7% is indeterminate [1]. Because symptom severity is not correlated with the severity of pathological acid reflux, normal ranges should be deemed as guidelines for interpretation rather than absolutes [1,21].

MII-pH data should at least include the type (acid, weakly acidic, weakly alkaline) and number of reflux episodes, bolus exposure index (%), bolus clearance time, acid exposure time (%), acid clearance time, total number of symptoms subdivided into symptom type, and symptom association. Normal ranges for MII-pH monitoring in children and adults have been reported (Table 3) [24-26]. Recently, normal values for preterm infants were suggested [24]. However, some weaknesses of this study include the prematurity of the patients, the small population size and the fact that all infants received tube feeding, which influences the higher number of reflux episodes [19]. Studies including a larger population are required to confirm the normal ranges in infants and children.

Table 3. Normal Values of Multichannel Intraluminal Impedance-pH Monitoring

Reference	Age	Subject (n)	MII reflux episodes (n)				BEI (%)	RI (%)
			Acid	WA	Alk	Total		
López-Alonso et al. [24]	12 d (32 wk, median gestation)	21	18 (52)	51 (98)	0 (NR)	71 (100)	0.73 (1.2)	5.59 (20.1)
Shay et al. [25]	39 y (22-62 y)	60	18 (59)	9 (26)	0 (1)	30 (73)	0.5 (1.4)	1.2 (6.3)
Zerbid et al. [26]	35 y (18-72 y)	68	22 (50)	11 (33)	3 (15)	44 (75)	0.8 (2.0)	1.6 (5.0)

Values are presented as median (range) or median (95th percentile).
MII: multichannel intraluminal impedance, WA: weakly acidic, Alk: weakly alkaline, BEI: bolus exposure index, RI: reflux index, NR: not reported.

SYMPTOM ASSOCIATION REPORTING

Because of the lack of normative MII-pH data, MII-pH monitoring is mainly used for symptom correlation in children. Symptom association analysis is a valuable method to establish possible associations between reflux and short-lived symptoms such as apnea, chest pain, regurgitation, and cough [21]. The results of combined MII-pH monitoring may support the correlation between reflux and symptoms through the use of several analytic methods, including the symptom index (SI), symptom sensitivity index (SSI), and symptom association probability (SAP). The analytic methods used to determine symptom-reflux associations are described in Table 4.

The SI is the simplest method to determine the percentage of symptoms that are associated with reflux events. However, when the number of reflux episodes is large or the number of symptoms is small, the SI tends to provide false-positive results. The SSI is defined as the percentage of symptom-associated reflux episodes. However, when the number of reflux episodes is small or the number of symptoms is small, the SSI tends to provide false-positive results. The SAP was developed to overcome these problems and is usually recognized as the strongest statistical parameter for symptom association analysis. Positive symptom association, which suggests causality between reflux and symptoms, is defined when both SI and SSI are positive or when SAP is positive [7,17,27,28].

However, the clinical utility of these parameters is still debated and certain limitations of these methods have been reported. First, registration of symptoms may be inaccurate because of the time delay associated with recording of symptoms in writing or pressing buttons, which can result in the underestimation of the number of symptoms. Second, a clear definition of the optimal time interval is lacking. The time interval of ±2 or ±5 minutes at a reflux episode as per symptom is generally used to demonstrate a time association by consensus. Third, an effective method to evaluate the symptom-reflux association in long-lived symptoms such as wheezing, bronchial hyper-reactivity, or laryngitis has not been defined. Fourth, whether these parameters conclusively prove symptom associations on the basis of assumptions and statistical probability remains unknown.

pH-ONLY ACID RELFUX EPISODES

"pH-only" episodes occur frequently in infants and they have a considerably influence on total esophageal acid exposure [21,29,30]. Studies conducted in symptomatic term infants found that impedance monitoring misses 9% to 40% of acid reflux episodes [31,32]. There are several possible reasons for these missed episodes such as insignificant bolus size, reflux esophagitis, slow pH drift caused by esophageal shortening, the residuals of acid MII reflux that were not completely cleared and short-column acid reflux episodes that do not meet the scoring rules by definition [21,33-36].

Currently, there is a debate as to whether pH-only episodes are important in the etiology of symptoms

Table 4. Methods of Analyzing Symptom Association

	SI	SSI	SAP
Definition	% of reflux-associated symptoms divided by total number of symptoms	% of symptom-associated reflux divided by total number of reflux	Calculation of the statistical relation between reflux and symptoms (Fisher's extract test)
Positive	50%	10%	95%
Pros	Simple, understandable; easy to calculate	Simple, understandable; easy to calculate	Use all parameters
Cons	Does not take into account the total number of reflux episodes, False(+)	Does not take into account the total number of symptoms, False(+)	Manual calculation is difficult

SI: symptom index, SSI: symptom sensitivity index, SAP: symptom association probability.

and should be included in the MII-pH analysis [30,37,38]. Rosen et al. [29] recommended that because pH-only episodes are common in pediatrics, they should be included in the MII-pH analysis. However, Loots et al. [17] showed that the inclusion of reflux episodes detected only by a pH probe reduced the ability of MII-pH monitoring to establish a positive symptom association. This result could be attributed to the fact that they analyzed all MII reflux episodes, including many pH-only episodes that were not associated with symptoms. By contrast, Shin et al. [7] performed symptom association analysis on the basis of MII-pH and pH monitoring separately and showed that the pH-only episodes can also lead to symptom association.

CONCLUSION

Although esophageal pH monitoring has major drawback not to detect nonacid reflux, it is still performed in many centers because it is readily available and cheap, and the automatic analysis can be interpreted according to normative values of RI. Combined MII-pH monitoring provides more information than pH monitoring alone because it can detect nonacid reflux and analyze the association between nonacid reflux and symptoms. Despite the fact that normal ranges in the pediatric population have not been defined, MII-pH monitoring has been used for symptom association analysis, especially for atypical symptoms. However, evidence of its use in this setting is still not available. Nonetheless, because pH monitoring is part of MII-pH, the use of MII-pH as a tool in standard clinical practice may increase and this method may replace pH-metry in the future.

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