Indications, Methodology, and Interpretation of Combined Esophageal Impedance-pH Monitoring in Children: ESPGHAN EURO-PIG Standard Protocol

*Tobias G. Wenzl, †Marc A. Benninga, †Clara M. Loots, ‡Silvia Salvatore, §Yvan Vandenplas, on Behalf of the ESPGHAN EURO-PIG Working Group

ABSTRACT

Aim: The aim of the study was to provide an updated position statement from the ESPGHAN European Pediatric Impedance Working Group on different technical aspects such as indications, methodology, and interpretation of multichannel intraluminal impedance-pH monitoring (MII-pH).

Methods: Evidence was used where available, but the article is based mainly on expert opinion and consensus.

Results: MII-pH provides more information than simple pH monitoring because reflux detection is not limited to acid reflux. Different companies provide commercialized MII-pH recording systems, making the method widely available and useable in daily clinical practice; however, the technique still has limitations: high cost, limited additional value regarding therapeutic implications, and lack of evidence-based parameters for the assessment of gastroesophageal reflux and symptom association in children.

Conclusions: MII-pH recording is a promising procedure needing further validation and development to increase its additional benefit over conventional investigation techniques. The added value of the technique regards mainly clinical circumstances in which nonacid or weakly acid reflux may be relevant such as persisting symptoms during antireflux treatment with proton pump inhibitors and feeding-related reflux; and assessing specific discontinuous symptoms thought to be associated with gastroesophageal reflux; and research.

Key Words: gastroesophageal reflux, multichannel intraluminal impedance, pH monitoring

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From the *Klinik für Kinder und Jugendmedizin, Universitätsklinikum der RWTH Aachen, Aachen, Germany, the †Department of Pediatric Gastroenterology and Nutrition, Emma Children's Hospital/AMC, Amsterdam, The Netherlands, the ‡U.O. Pediatria, Università dell'Insubria, Ospedale ''F. Del Ponte,'' Varese, Italy, and the §University Children's Hospital, Brussels, Belgium.

Address correspondence and reprint requests to Priv-Doz Dr med Tobias G. Wenzl, FRCPCH, Klinik für Kinder- und Jugendmedizin, Universitätsklinikum der RWTH Aachen, Pauwelsstr 30, 52074 Aachen, Germany (e-mail: twenzl@ukaachen.de).

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Multichannel intraluminal impedance (MII) is a procedure for measuring the movement of fluids, solids, and air in the esophagus. Combined MII and pH recording detects liquid reflux, independent of its pH, and gas episodes. MII-pH has been available with pediatric catheters for use in children of all age groups since 2002. The present North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition–European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines on pediatric gastroesophageal reflux (GER) state that because ''MII-pH monitoring detects acid, weakly acid, and nonacid reflux episodes, it is superior to pH monitoring alone for evaluation of the temporal relation between symptoms and GER'' (1); however, this statement does not endorse that the correlation between symptoms and GER is good. Moreover, there is considerable diversity in performance and interpretation of MII-pH recording between users (2). Inter- and intraobserver reproducibility studies of the visual human analysis have shown diverging results (2,3). The aim of the European Pediatric Impedance Group, a working group of the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN), is to establish standards for the indications, methodology, and interpretation of combined impedance-pH measurements (MII-pH) in children of all age groups. The literature was reviewed by searching available databases, conference proceedings, and personal resources. In the preparation of this protocol, the European Pediatric Impedance Group referred to existing protocols of the German Pediatric Impedance Group (G-PIG) (4).

INDICATIONS

MII is mainly of interest because it also measures GER that is not acid. The main differences between pH and MII-pH are listed in Table 1. GER symptoms under investigation can generally be divided into gastrointestinal, pulmonary/laryngopharyngeal/ear-nose-throat, and neurological indications (1). In principle, the indications for MII-pH monitoring are the same as the indications for pH metry: to quantify reflux in patients with mainly extra-esophageal symptoms, to measure GER in patients not responding to antireflux treatment, and in research. If MII-pH monitoring would not be more expensive than pH metry, and if interpretation would be similar, there would be no longer an indication for simple pH metry because the latter is part of the MII-pH recording. MII-pH is believed to be particularly useful for the assessment of specific discontinuous symptoms, such as cough, that are possibly associated with mainly nonacid or weakly acid GER. MII-pH can be performed off and/or on treatment and on either continuous or bolus-based enteral feeds, which means that reflux during meals and during postprandial periods should preferably be taken into account.

TABLE 1. Comparison between pH monitoring and impedance

Parameter	pH monitoring	MII-pH
Acid GER	Yes	Yes
Nonacid GER	Blind	Yes
Superimposed acid reflux	Blind	Yes
Gas reflux	Blind	Yes
Height of reflux	1 or 2 levels	6 levels
Chemical clearance	Yes	Yes
Bolus clearance	Blind	Yes
Postprandial GER	Blind	Yes

GER = gastroesophageal reflux; MII = multiple intraluminal impedance.

RECORDING DEVICES AND SOFTWARE

MII-pH measurements are feasible in every age group, from premature infants to adolescents. Movements of gas and liquid bolus are measured. Acid (pH < 4), weakly acidic (pH 4–7), or nonacid (pH > 7) bolus movements, or pure gas, or mixed (gas and liquid) episodes are identified. Ambulatory and stationary systems from different manufacturers are available and can be used in children (Table 2). Stationary systems offer the possibility of recording MII-pH synchronous and integrated with the recording of many other parameters such as oxygen saturation, heart and respiratory rate, and esophageal (high resolution) manometry. Portable ambulatory devices offer superior patient comfort and better document reflux events during normal daily activities/conditions. Some devices allow simultaneous recording of different parameters, such as manometry, in combination with MII-pH. Objective cough recording with esophageal manometry in combination with MII and pH monitoring improves symptom association analysis (5). Both acid and weakly acid GER may precede cough in children with unexplained cough, but cough does not induce GER (5).

MII-PH CATHETERS AND THEIR PREPARATION

Many different catheters of varying construction and differing pH electrodes (antimony, ISFET [ion-sensitive field-effect transistor], glass) are commercially available. For standard measurements, patient-length appropriate catheters, with at least 6 impedance and 1 distal (mostly antimony) pH channel, should be used. MII-pH catheters have a diameter of 2.13 mm (6.4 F). Different age (height)-appropriate impedance catheters are available: infant (height <75 cm), pediatric (height >75 cm and <150 cm), and adult (height >150 cm). The distance between the impedance rings and the location of the pH sensor differ among different catheters (according to the height of the patient and manufacturing variability). In infant catheters, impedance rings are 1.5-cm apart, and if the probe includes a single esophageal pH electrode, this is positioned in the middle of the last MII channel, 0.75 cm above the first ring. In the pediatric and adult catheters, the rings are 2 cm far from each other and the pH sensor is in the center of the most distal impedance channel or the one immediately proximal to it, respectively. Although antimony electrodes are less accurate than glass or ISFET electrodes (6), antimony electrodes are the most popular because of cost (vs glass) and ease of insertion (vs ISFET). There is no universal recommendation regarding whether to use single- or multiple-use catheters. Single- or multiple-use catheters can be used according to investigator or patient preference, national standards and reimbursement strategies, hygiene requirements, and regulations. Multiple-use catheters must be sterilized and processed according to the recommendations of the manufacturer. Therefore, single-use catheters are preferred increasingly often. Catheters with internal reference electrode are more convenient because no separate external skin electrode is required. The internal reference electrode is located at the tip of the catheter, which is (depending on the type of electrode) 3 to 5 cm distal to the distal pH sensor and may cross the lower esophageal sphincter, thereby potentially increasing the number of GER episodes (7).

The pH electrode on the combined MII-pH catheter should be calibrated according to the instructions of the manufacturer with 2 different pH solutions. For external reference catheters, this needs to be done with the external reference electrode fixed on the child, and its finger needs to be in the calibration fluid together with the electrode. This is not necessary for catheters with internal reference electrodes. pH electrodes that show unstable calibration results should not be used because this indicates a potential risk for a significant pH drift. During the routine calibration before each MII-pH study, each impedance electrode is tested for conductivity and intactness. If calibration does not provide proper results, the catheter should not be used.

MII-pH catheters are passed transnasally, preferably without sedation, although the use of local anesthesia (eg, intranasal anesthetic spray) may be beneficial in some children. Gel is often used to ease the passage through the nostrils; however, the gel should not be placed directly on the antimony electrode because the presence of gel on the antimony probe may decrease its accuracy. The pH electrode should be positioned 2 vertebrae above the diaphragm at the level of the vertebral column. Strobel formula ($0.252 \times$ body length [cm] + 5) (8) can be used to estimate appropriate probe location; however, investigators must be aware that this formula was developed for infants and hence becomes more imprecise with increasing height because the formula overestimates esophageal length. Therefore, correct catheter position is confirmed by preference by fluoroscopy or x-ray. If the patient also needs endoscopy, then the catheter may be placed under visual endoscopic inspection. Manometry allows to measure the distance at which the catheter should be placed above the lower esophageal sphincter.

The equipment and the MII/pH catheters are expensive. Although the cost differs from country to country, an impedance device may be roughly estimated at €15,000 and an impedance catheter with antimony or ISFET sensors at approximately €150. The catheters are single use. In many countries, there is no appropriate reimbursement for the MII-pH measurement. Reading and interpretation of a tracing by an experienced person take easily ≥1 hour, resulting in a relevant additional cost.

TABLE 2. List of MII-pH brands available in the marketplace

Brand of MII-pH	Software
Sandhill	BioView analysis
MMS	Ohmega software
Vizion	Vizion software

MII = multiple intraluminal impedance.

PATIENT INSTRUCTION AND PROTOCOL

As for pH-metry, diagnostic patient investigations are preferably performed for 24 hours because of the difference in incidence and duration of reflux episodes during meal, postprandial, and fasting periods, and the differences between vertical or horizontal position, or awake and asleep. Thorough patient, caregiver, and/or staff instructions on symptom documentation and recording are mandatory to obtain good-quality data for study interpretation. Relevant symptoms should be agreed on before the study begins and can be assigned to ''event'' buttons on the recording device that then should be pressed with the occurrence of each symptom. In addition, some investigators recommend completing a written symptom diary. This recording of symptoms needs to include the time shown on the recorder to allow the evaluation of symptom association. The minimum data that should be documented during any study include mealtimes (beginning and end), position (prone and supine), symptoms, and other relevant events (eg, correction of catheter position, disconnection of the skin electrode). Clear instructions to avoid ''acid'' foods and carbonated beverages (eg, Coca-Cola) must be given before the measurement because they make the interpretation more complex. The reactivity of the pH electrodes is also influenced by temperature; therefore, extremely hot or ice-cold drinks and food should preferably be avoided; however, because patients (and/or parents) are asked to record all of the events in a diary and because impedance differentiates between a swallow and a reflux (not the case with simple pH-metry), the ingestion of acid foods and beverages can easily be recognized and thus deleted from the tracing. Symptoms that are not under investigation should not be included. If they are entered as symptom events, then they should be excluded before analysis because their inclusion can cause false results regarding symptom association.

Recent data show that manual documentation of events in a diary or even using the event button has limitations regarding the precision of the documentation (4). Because demonstrating a temporal relation between GER and extraesophageal manifestations is clinically relevant, a measurement providing objective information with respect to this relation is important. A MII-pH recording provides this information. MII is mainly of interest because it also measures GER that is not acid. It means that reflux during meals and during postprandial periods is also taken into account.

ANALYSIS, STATISTICS, AND REPORTING

At the end of the measurement, data are downloaded to a computer, which should have a reliable backup system. Analysis uses software aided by different modules included in every standard MII-pH software package. Although to date no automated analysis is fully validated for children, most MII-pH users start the tracing analysis with the automated analysis, and then manually-visually go through the study confirming, adding, and/or deleting reflux events. Because it is ethically not possible to perform MII-pH recordings in asymptomatic healthy children, real normal ranges are not available, although the G-PIG tried to do so (4). The G-PIG published the largest series of pediatric impedance tracings (700 MII-pH from children 3 weeks–16 years of age presenting with symptoms suggestive of GER disease) and defined as abnormal MII study if the measurement fulfils the following criteria: symptom index (SI) $\geq$50% or a high number of reflux episodes (arbitrarily defined as >70 episodes in 24 hours in patients ages 1 year or older and >100 episodes in those younger than 1 year) (4). Normal ranges in adults have been published (Table 3). Consensus on definitions for different parameters has been reached. Regarding impedance, a bolus-liquid reflux is defined as a retrograde drop in impedance of at least 50% of the baseline in at least 2 distal impedance channels (3 consecutive rings). The end of a reflux episode is defined as the moment when the impedance value returned to at least 50% of the initial (baseline) value. Gas-only reflux is characterized by an increase in impedance >3000 Ohm in any 2 consecutive impedance sites with 1 site having an absolute value >7000 Ohm. Mixed reflux events are a combination of both liquid and gas pattern; however, visual manual analysis does not always permit the application of these definitions, which were developed for automatic analysis. Automated analysis is generally tuned to high sensitivity, resulting in rather poor specificity. Because inter- and intraobserver variability remains relatively high, even among experienced experts (2), a refined and validated automated analysis is required for clinical practice. This would ensure reproducibility and reliability and would significantly decrease the time needed for analysis.

All of the documented diary events should be entered into the study before running an automated analysis; however, when correlating diary data with GER events, one must consider that diary data recorded by the parent or caregiver may be imprecise due to the time delay in pressing buttons or recording symptoms in writing. In general, a time interval of ±2 minutes before and after a reflux event is used as accepted time interval to demonstrate a time association; however, the ''2 minutes'' is chosen by consensus but is not evidence based. Experience has shown that automatic analysis presents difficulties in recognizing GER during meals; therefore, meals are often not considered. Because reflux does occur during meals, it may be relevant to study reflux during meals, however.

The most frequently analyzed and calculated parameters are listed in Table 4. After completion of the GER event analysis, the report should at least include the total number of GER events with the number of acid/weakly acidic/nonacid GER events (and eventually gas episodes), number of GER reaching the most proximal impedance segment, total acid clearance time, total acid exposure index (%) (formerly known as reflux index), total bolus clearance time, total bolus exposure index (%), total number of symptoms subdivided into symptom type, and each of the above with a temporal association between symptom and reflux event.

Symptom association reporting should include the number of symptoms associated with (different types of) GER, number of symptoms not associated with GER, number of GER episodes associated with symptoms, and number of GER events not associated with symptoms.

With these data, different statistical approaches have been used for further analysis (9,10). The SI (reported as %) is the percentage of GER-associated symptoms divided by the total number of symptoms. It was arbitrarily decided for adults that a high (or ''positive'') SI points toward the symptoms being reflux

TABLE 3. Published adult normal values of 24-hour MII-pH

Reference	No. subjects	Country	Acid reflux	WAR	AlkR	Total no. reflux	MACT	MBCT	BEI (%)
Shay et al (20)	60	United States	18 (59)	9 (26)	0 (1)	30 (73)	23 s	11 s	0.5 (1.4)
Zerbib et al (21)	68	France and Belgium	22 (50)	11 (33)	3 (15)	44 (75)	34 s	11 s	n.r. (2)
Zentilin et al (22)	25	Italy	18 (51)	14 (38)	4 (18)	16 (48)	28 s	12 s	n.r.

Numbers are presented as median (95th percentile). AlkR = weakly alkaline; BEI = bolus exposure index; MACT = mean acid clearance time; MBCT = mean bolus clearance time; MII = multiple intraluminal impedance; n.r. = not reported; WAR = weakly acidic reflux.

TABLE 4. Definitions of reflux parameters

Liquid MII-reflux episode: decrease in impedance with ≥50% from baseline
Acid MII reflux: with a pH <4.0
Nonacid reflux: with a pH ≥4.0
Weakly acid reflux: with a pH ≥4.0 but <7.0
Weakly alkaline reflux: with a pH ≥7.0
Gas MII-reflux episode: sharp increase of impedance >3000 Ohm
Mean bolus clearance time: time needed for a bolus to be cleared from the esophagus
Bolus exposure index: the percentage of time that a bolus is present in the esophagus
Mean acid clearance time: time needed for acid to be cleared from the esophagus (previously better known as the reflux index)

MII = multiple intraluminal impedance.

associated, with a SI of 50% usually being used as the lower limit of significance (11); however, it is important to be aware that studies with a small number of symptoms and/or a high number of GER episodes will have a tendency to give a false-positive SI. In other words, this parameter has a high sensitivity but low specificity. The symptom sensitivity index (SSI, reported as %) is the percentage of symptom-associated GER events divided by the total number of GER events. Again, studies with a high number of symptoms and/or a small number of GER episodes have a tendency to give a falsely high SSI. A value of >10% is generally accepted as clinically significant (12). For the calculation of the symptom association probability (SAP, reported as %), the total measuring time is subdivided into 2-minute intervals, and a contingency table with 4 fields is established: number of intervals with GER and symptom, number of intervals with GER and without symptom, number of intervals without GER and with symptom, and number of intervals without GER and symptom. The Fisher exact test is then used for the statistical analysis of correlation. A positive SAP (>95%) is interpreted as a good temporal association between GER and the recorded symptom (13). SAP is generally accepted as the strongest statistical approach for the analysis of GER symptom association because it is least influenced by the absolute number of GER events and number of symptoms. The minimum number of symptoms to obtain an accurate/reliable SAP is still debated but may vary for different symptoms (13).

There are also some drawbacks to these parameters:

1. Registration of symptoms may be the weakest aspect; it is clear from studies that ‘‘pressing the event button’’ or ‘‘writing the symptoms down in a diary’’ underscores the number of symptoms; the older the child, the less meticulous parents seem to become (14).
2. There are no data on the optimal time frame that should be used. These time frames may differ from symptom to symptom (and, for example, be different for ‘‘apnea’’ [short time frame] and ‘‘wheezing’’ [probably no time frame]) and have not been validated in children.
3. SI, SSI, and SAP are based on a ‘‘percentage’’ of symptoms associated in time with a reflux event and thus miss the ‘‘2 reflux events on a 24-hour registration that are associated with a significant life-threatening event’’; in other words, individual experience-based interpretation taking into account clinical relevance remains the cornerstone.
4. For some symptoms (eg, wheezing, bronchial hyperreactivity, laryngitis) with a longer or perhaps different GER–symptom relation, temporal symptom association may not be readily achieved.

In general, the demonstration of a temporal association is relevant for symptoms of short duration (eg, cough, apnea, desaturation), whereas for symptoms of long duration (eg, laryngitis, hoarseness, bronchitis), a global interpretation of the MII-pH recording is more relevant. Up to now, only extremely limited double-blind placebo-controlled prospective therapeutic trials have been conducted in children suspected of having extraesophageal symptoms as a consequence of GER. As long as evidence is missing, recommendations regarding optimal conditions and interpretation of the diagnostic procedures cannot be made.

Baseline impedance is a relative, recently developed parameter that is related to mucosal integrity or conductivity. Baseline impedance is lower in patients with esophagitis than in patients with nonerosive reflux disease (15). Proton pump inhibitor treatment results were shown to increase baseline impedance (16); however, baseline impedance is influenced by the number of impedance events and differs with age (17).

MII-pH reports should include the type, method, and results of the chosen analysis, an interpretation of these results in light of the clinical history, and a recommendation for treatment or further investigations. To date there is no validated standardized method to precisely describe the temporal association between GER and symptoms. Analysis and interpretation of these studies should only be carried out by those with adequate training and experience in impedance analysis.

DIFFICULTIES, COMPLICATIONS, AND FUTURE

Although it is not common practice to obtain written informed consent, there are rare but potential complications that parents and guardians should be made aware of, for example, technical failure (device or catheter), probe misplacement (height, bronchus), and mucosal trauma (bleeding, laceration). The causes and number of these complications are comparable with conventional pH-only monitoring. The incidence of complications of MII-pH is low. It is necessary to obtain ethical approval along with written informed consent if results of the measurement are used for research purposes. This allows use of anonymous data for data pooling in single or multicenter protocols (ie, ‘‘process documentation’’).

An area of future interest could be a comparison between MII-pH and reflux scintiscanning (measuring GER during a meal and 1 hour postprandial). The literature shows an extremely poor correlation between acid reflux measured with pH-metry and reflux episodes detected with scintigraphy (18). The combination of MII with videofluoroscopy and high-resolution manometry may be helpful to assess pharyngeal function because bolus movements are visualized, whereas pressure and movements of liquid and air are recorded (19). Lastly, the combination of MII and other polygraphic recordings such as heart rate and saturation should be developed further, allowing better evaluation of temporal relations among heart rate and apnea and GER.

CONCLUSIONS

MII-pH recording provides more information than simple pH measurement because it allows the study of non-acid reflux and the temporal association between symptoms and nonacid reflux. Further validation of the optimal time frames and incidence of symptom-impedance event correlation is needed. Whether combined esophageal pH and impedance monitoring will provide data that are sensitive to variations in disease severity, inform prognosis, or predict response to therapy in pediatric patients has yet to be determined (1). As long as there is no effective medical therapy for weakly acid and nonacid reflux, the clinical relevance of measuring these types of reflux remains debatable. There are no data on the results of antireflux surgery based solely on the detection of weakly acid and weakly alkaline reflux with MII. MII-pH recording is an investigation technique of great potential interest, but standardization of material and interpretation needs to be developed further before a wide routine diagnostic use can be recommended. The major indications of the technique can be summarized in the following areas: clinical circumstances in which nonacid or weakly acid reflux may be relevant such as persisting symptoms during antireflux treatment with proton pump inhibitors and feeding-related reflux; diagnosis of differential diagnoses of reflux disease such as rumination syndrome; assessing specific discontinuous symptoms believed to be associated with GER; and research. MII still has the following limitations: high cost; limited contribution to medical therapeutic implications; and lack of evidence-based parameters for the assessment of GER and especially symptom association in children. The authors have indicated in the present study different high-priority areas for further research.

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APPENDIX

Additional members of the Euro-PIG working Group: Gigi Veereman-Wauters (University Children's Hospital, Brussels, Belgium); Kasper Dalby (Hans Christian Andersen Children's Hospital, Odense University Hospital, Odense, Denmark); Lena Grahnquist (Paediatric Gastroenterology and Nutrition, Astrid Lindgren Children's Hospital, Karolinska University Hospital, Stockholm, Sweden); Denisa Pilic (University Hospital Bochum, Bochum, Germany); Michael A. Thomson (Sheffield Children's Hospital, Sheffield, UK); Michiel P. van Wijk (Emma Children's Hospital/AMC, Amsterdam, The Netherlands).