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ORIGINAL ARTICLE

Clinical Trials Study

Comparison of multichannel intraluminal impedance-pH monitoring and reflux scintigraphy in pediatric patients with suspected gastroesophageal reflux

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Abstract

AIM

To evaluate the agreement of multichannel intraluminal impedance-pH monitoring (MII-pHM) and gastroesophageal reflux scintigraphy (GES) for the diagnosis of gastroesophageal reflux disease.

METHODS

Seventy-five consecutive patients with suspected



gastroesophageal reflux disease (GERD) underwent 24-h combined MII-pHM recording and one hour radionuclide scintigraphy during the course of the MIIpHM study. Catheters with 6 impedance channels and 1 pH sensor were placed transnasally. Impedance and pH data analysis were performed automatically and manually. For impedance monitoring, reflux was defined as a retrograde 50% drop in impedance, starting distally and propagating retrogradely to at least the next two more proximal measuring channels. Reflux index (RI, percentage of the entire record that esophageal pH is < 4.0) greater than 4.2% for pHM and number of refluxes more than 50 for 24 h for MII were accepted as positive test results. At scintigraphy, 240 frames of 15 seconds duration were acquired in the supine position. Gastroesophageal reflux was defined as at least one reflux episode in the esophagus. After scintigraphic evaluation, impedance-pH recordings and scintigraphic images were evaluated together and agreement between tests were evaluated with Cohen's kappa.

RESULTS

Sufficient data was obtained from 60 (80%) patients (34 male, 56.7%) with a mean age of 8.7 ± 3.7 years (range: 2.5-17.3 years; median: 8.5 years). Chronic cough, nausea, regurgitation and vomiting were the most frequent symptoms. The mean time for recording of MII-pHM was 22.8 \pm 2.4 h (range: 16-30 h; median: 22.7 h). At least one test was positive in 57 (95%) patients. According to diagnostic criteria, GERD was diagnosed in 34 (57.7%), 44 (73.3%), 47 (78.3%) and 51 (85%) patients by means of pHM, MII, GES and MII-pHM, respectively. The observed percentage agreements/k values for GES and pHM, GES and MII, GES and MII-pHM, and MII and pHM are 48.3%/-0.118; 61.7%/-0.042; 73.3%/0.116 and 60%/0.147, respectively. There was no or slight agreement between GES and pHM alone, MII alone or MII-pHM. pH monitoring alone missed 17 patients compared to combined MII-pHM. The addition of MII to pH monitoring increased the diagnosis rate by 50%.

CONCLUSION

No or slight agreement was found among pH monitoring, MII monitoring, MII-pH monitoring and GES for the diagnosis of gastroesophageal reflux disease.

Key words: Gastroesophageal reflux disease; Children; Multichannel intraluminal impedance; Esophageal pH monitoring; Scintigraphy

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Core tip: Gastroesophageal reflux (GER) is usually physiological, common in childhood and defined as GER disease (GERD) when it causes troublesome symptoms and/or complications. Unfortunately, the ideal diagnostic method for GERD has not been

identified yet. Each method has its own advantages and disadvantages. This study aimed to evaluate the agreement of multichannel intraluminal impedance-pH monitoring and gastroesophageal reflux scintigraphy, which is used frequently all over the world for the diagnosis of GERD. No or slight agreement between tests was found. New diagnostic standards for scintigraphy in GERD should be defined.

Uslu Kızılkan N, Bozkurt MF, Saltık Temizel IN, Demir H, Yüce A, Caner B, Özen H. Comparison of multichannel intraluminal impedance-pH monitoring and reflux scintigraphy in pediatric patients with suspected gastroesophageal reflux. *World J Gastroenterol* 2016; 22(43): 9595-9603 Available from: URL: http://www.wjgnet.com/1007-9327/full/v22/i43/9595.htm DOI: http://dx.doi.org/10.3748/wjg.v22.i43.9595

INTRODUCTION

Gastroesophageal reflux (GER) is defined as the passage of gastric contents into the esophagus which is usually physiological and common in childhood^[1]. It is defined as gastroesophageal reflux disease (GERD) when it causes troublesome symptoms and/or complications. It is important to distinguish physiological GER events from GERD. A variety of tests for the diagnosis of GERD are available: 24-h esophageal pH monitoring (pHM), multichannel esophageal intraluminal impedance testing (MII), combined MII and pHM (MII-pHM), gastroesophageal reflux scintigraphy (GES), upper gastrointestinal barium contrast radiography, esophagoscopy and biopsy, motility studies and ultrasonography^[1,2]. Each of these tests for the diagnosis of GERD in the pediatric population has advantages and limitations and none of them is ideal. In children old enough to describe their symptoms reliably, the diagnosis of GERD can be made clinically and it is generally not necessary to perform diagnostic tests.

MII-pHM detects acidic, weakly acidic and nonacidic reflux episodes, can accurately detect the height of the refluxate, is able to determine whether the refluxate is liquid, gas or mixed (both liquid and gas), can still measure symptom association with GER even while the patient is taking acid-suppression medications and is superior to pH monitoring alone for evaluation of the temporal relationship between symptoms and GER. However, MII/pHM is expensive and time consuming^[1,3-10]. Additionally, the specificity of automated analysis (AA) is low, inter- and intraobserver variability is large and agreement with automated analysis is poor [11-13]. Manual analysis may take 3 h depending on the experience of the investigator and the number of reflux episodes to be analyzed. Another limitation of MII-pHM use is that it is not commonly available and normal values for all

age groups have not yet been established^[5-9]. Despite these limitations, studies in the last decade have revealed that this method can be the golden diagnostic method for GER detection^[14].

Nuclear imaging scintigraphy is more widely available worldwide than pHM and/or MII-pHM. It is simple, noninvasive, can detect not only reflux event but also aspiration, abnormal esophageal contractions and delayed gastric emptying, it usually takes one hour to perform the procedure and is accepted by many pediatricians as an additional diagnostic test for the diagnosis and follow-up of GER in infants and children. It also allows quantification of gastric emptying and detection of reflux aspiration into the bronchial system. It also has some disadvantages as the performance and interpretation of the test can show some variations between centers as the standards of the test are poorly established. Showing only postprandial refluxes independently of pH lowers its diagnostic value as it is already known that GER occurs mostly in the postprandial period^[15-22]. The European (ESPGHAN) and North American (NASPGHAN) Societies for Pediatric Gastroenterology, Hepatology and Nutrition do not recommend GES in the routine diagnosis and management of GER in infants and children because of the low sensitivity of the test^[1].

The primary aim of this study is to evaluate the agreement of GES, which is used frequently all over the world for the diagnosis of GERD and MII-pH monitoring. We also aimed to investigate the sensitivity and specificity of pHM alone and GES compared to MII-pHM and vice versa.

MATERIALS AND METHODS

Patient population

Seventy-five consecutive patients referred to Hacettepe University Pediatric Gastroenterology, Hepatology and Nutrition Unit for suspected GERD were enrolled in the study. Patients younger than 24 mo were excluded.

Multichannel intraluminal impedance-pH monitoring

All patients underwent 24-h combined MII-pHM recording (MMS Ohmega Ambulatory Impedance and pH Recorder, the Netherlands). All of the subjects had been taken off proton pump inhibitors, histamine-receptor antagonists and prokinetics at least 72 h before the study. Impedance catheters with 7 impedance (6 channels) and 1 pH sensors (Unisensor, Attinkon, Switzerland) were used. A pH sensor was placed at 3 cm while impedance sensors were placed at 1-3-5-7-9-11-13 cm. Before the procedure, the pH recorder was calibrated using buffered solutions of pH 1.0 and pH 7.0, as specified by the manufacturer. The catheter was placed through the nose and the pH sensor was placed at 87% of the nares-lower esophageal sphincter distance^[23]. Placement of the pH

sensor was confirmed by radiographic evaluation. The catheter was connected to a data logger which stores data from impedance channels with a frequency of 50 Hz and pH sensor of 1 Hz. Children received their regular diets except acidic drinks and were asked to keep at least 4 h intervals between meals.

Impedance and pH data analysis were performed automatically by using MMS Investigation and Diagnostic Software®, the Netherlands. All tracings were also manually reviewed by investigators (HÖ, NUK) experienced in interpretation of pH-impedance recording. For impedance monitoring, reflux was defined as a retrograde 50% drop in impedance, starting distally and propagating retrogradely to at least the next two more proximal measuring channels^[24]. A GER episode was then defined as acidic (pH < 4), weakly acidic (pH between 4 and 7) or alkaline (pH > 7) according to the associated pH change. Physical composition of the refluxate was also identified and MII detected episodes were divided into liquid and mixed. Reflux index (RI, percentage of the entire record that the esophageal pH is < 4.0) greater than 4.2% for pHM and number of refluxes for 24 h more than 50 for MII were accepted as positive test results[24-28].

Gastroesophageal reflux scintigraphy

The scintigraphy was performed during the course of the MII-pH study after a fasting of 4 h using technetium-99m tin colloid (7 microCi/kg body weight or 0.74 megabecquerel/kg bw, minimum dosage 200 microCi and maximum dosage 500 microCi) administered orally in a mixture of thick orange juice for patients older than 3 years and milk or formula for patients younger than 3 years old (20 mL/kg body weight, maximum 300 mL). After swallowing 30 mL of radiolabeled test liquid, the patient was given the remaining portion of unlabeled orange juice or milk/formula. Patients lay in the supine position under the gamma camera for 1 h and were kept immobile with velcro straps. Two hundred and forty frames of 15 s duration were acquired in a 64 \times 64 matrix. At the beginning of scintigraphy, the time shown by the ambulatory impedance-pH recorder was recorded. All results were visually analyzed for the occurrence of reflux by two investigators (Bozkurt MF, Caner B). No quantitative analysis was performed. Gastroesophageal reflux was defined as at least one reflux episode in the esophagus defined as linear activity emerging from stomach to esophageal trajectory in dynamic scintigraphic imaging^[15].

After scintigraphic evaluation, impedance-pH recordings and scintigraphic images were evaluated together (Uslu Kızılkan N, Özen H, Bozkurt MF, Caner B) and agreement among three tests were recorded.

Ethical permission

Hacettepe University Clinical Researches Ethics Board approved the study (B.30.2.HAC.0.01.00.05/222).



Table 1 Comparison of pH monitoring and gastroesophageal reflux scintigraphy

	Gastroesophageal scintigraphy positive	Gastroesophageal scintigraphy negative	Total
pH monitoring	25	9	34
positive pH monitoring negative	22	4	26
Total	47	13	60

Kappa value= -0.118 [P = 0.302, 95%CI: -0.232-(-0.004)]; Overall percent agreement = 48.3%; When pH monitoring is considered as reference test, positive percent agreement = 73.5% and negative percent agreement = 15.4%.

Written consent was obtained from all of the parents and patients old enough to understand and sign the informed consent form.

Statistical analysis

Parametric data are presented as mean ± SD unless otherwise stated. Agreement between tests for the diagnosis of GERD was assessed by using Cohen' s kappa $(\kappa)^{[29]}$: values ≤ 0 indicates no agreement, 0-0.20 slight agreement, 0.21-0.40 fair agreement, 0.41-0.60 moderate agreement, 0.61-0.80 substantial agreement, and 0.81-1 almost perfect agreement. Overall percent agreement, positive (PPA) and negative (NPA) percent agreements are calculated where needed. Sensitivity, specificity, positive and negative predictive values of the tests are also calculated according to the considered gold standard diagnostic method (MII-pHM or GES). Statistical significance was defined as P < 0.05. SPSS version 16 was used for statistical analysis. The statistical methods of this study were reviewed by Prof. Ergun Karaagaoglu from the Department of Biostatistics, Hacettepe University Faculty of Medicine.

RESULTS

Seventy-five children were enrolled in the study. The duration of GER symptoms was 10.8 ± 9.9 mo (range: 1-48 mo; median: 8.0 mo). Chronic cough, nausea, regurgitation and vomiting were the most frequent symptoms.

The tests were well tolerated by all with no complications. Fourteen patients were excluded for artifacts and technical problems in MII-pH tracings (eight non-interpretable traces due to artifacts or displacement of the probe, four for technical reasons and two premature termination of the recording due to battery problems) and one patient because of an unsuccessful scintigraphic procedure. Sufficient data was obtained from 60 (80%) patients (34 male, 56.7%) with a mean age of 8.7 \pm 3.7 years (range: 2.5-17.3 years; median: 8.5 years). The mean time for recording of MII-pHM was 22.8 \pm 2.4 h (range:

Table 2 Comparison of multichannel intraluminal impedance monitoring and gastroesophageal reflux scintigraphy

	Gastroesophageal scintigraphy positive	Gastroesophageal scintigraphy negative	Total
MII monitoring	34	10	44
positive MII monitoring negative	13	3	16
Total	47	13	60

Kappa value = -0.042 (P = 0.741, 95%CI: -0.17-0.086); Overall percent agreement = 61.7%; When MII monitoring is considered as a reference test, positive percent agreement = 77.3% and negative percent agreement = 18.8%. MII: Multichannel intraluminal impedance.

16-30 h; median: 22.7 h).

At least one test was positive in 57 (95%) patients and three patients had negative results for all of the tests. Eighteen patients (30%) had positive test results for all three tests, while 30 (50%) patients had positive results for 2 of the tests and 9 (15%) had positive results for only 1 test. According to the above mentioned criteria, gastroesophageal reflux disease was diagnosed in 34 (57.7%), 44 (73.3%), 47 (78.3%) and 51 (85%) patients by means of pHM, MII, GES and MII-pHM, respectively.

The mean reflux index was $6.0\% \pm 6.9\%$ (range 0.1-38.4) and mean reflux number 70.6 ± 83.4 (range 6-481) with pH monitoring. The mean number of reflux episodes > 5 min was 2.2 ± 3.3 (range, 0-19). Overall, 3879 (mean 64.6 ± 29.8 , range: 18-146) GER events were detected with MII monitoring (liquid 1169, 30.1% and mixed 2710, 69.9%) and 1751 (45.1%) of them were characterized as acidic, 1618 (41.7%) as weakly acidic and 510 (13.2%) as alkaline. Also, we observed that 32.9% of refluxes reached the proximal esophagus and 41.2% of them were nonacidic.

During the 1 h simultaneous recording period, 880 reflux episodes were detected with GES and/ or MII-pHM. GES showed 770 reflux frames in 47 patients, only 142 of them (18.4%) were detected simultaneously with both techniques. Six hundred and twenty-eight episodes were detected only with GES and 110 only with MII-pHM (kappa = -0.27, P < 0.0001).

Tables 1-4 show comparisons of GES and pHM, GES and MII, GES and MII-pHM, MII and pHM, respectively. The observed percentage agreements/k values for the above comparisons are 48.3%/-0.118, 61.7%/-0.042, 73.3%/0.116 and 60%/0.147, respectively. pH monitoring alone missed 17 patients compared to combined MII-pHM. Therefore, the addition of MII to pH monitoring increased the diagnosis rate by 50%.

Assuming MII+pH monitoring or GES as the gold standard for GER diagnosis, sensitivity, specificity, positive and negative predictive values for pHM, MII,

Table 3 Comparison of multichannel intraluminal impedance/pH monitoring and gastroesophageal reflux scintigraphy

	Gastroesophageal scintigraphy positive	Gastroesophageal scintigraphy negative	Total
MII-pHM positive	41	10	51
MII-pHM negative	6	3	9
Total	47	13	60

Kappa value 0.116 (P = 0.357, 95%CI: -0.01-0.24); Overall percent agreement = 73.3%; When MII-pHM is considered as reference test, positive percent agreement = 80.4% and negative percent agreement = 33.3%. MII-pHM: Multichannel intraluminal impedance-pH monitoring.

MII-pHM and GES are shown in Table 5.

DISCUSSION

Gastroesophageal reflux is a common, challenging problem for pediatricians. It is important to differentiate physiological GER from GERD, which may cause severe complications, to decide who needs treatment^[1]. Both pHM^[30,31] and radionuclide^[32] studies for diagnosis of GERD go back more than 40 years. Esophageal intraluminal pHM became more popular with the development of a computer based system for the recording and automatic analysis of the data^[33] and was accepted as the gold standard for diagnosis of GERD for years. Later on, MII was developed and posited as the future standard for reflux detection and monitoring^[34]. Although the combined MII-pHM has advantage over pHM alone, it has some disadvantages as mentioned above^[1,4,11,14,35].

Another problem with pHM and MII is the absence of normal values in the pediatric age range. Currently no evidence based pediatric normal values exist. The ESPGHAN and NASPGHAN guidelines consider a RI > 7% as abnormal, a RI < 3% as normal, and between 3% and 7% as indeterminate^[1]. In this study, a RI value > 4.2% was accepted as abnormal^[27,36]. Currently, the "true" normal ranges for MII are not available for infants and children due to the fact that it is not ethical to perform MII-pHM on asymptomatic, healthy children. In children referred for GERD evaluation, the mean retrograde bolus movement numbers were reported as between 31 and 35, respectively^[27]. However, all were sick children and they do not represent healthy children. The reported number of reflux events (95th percentile) in healthy adults ranged from 48 to 75 per day and the age did not affect the number^[24,26,28]. In healthy adults consuming a Mediterranean diet, the total numbers of reflux events was 48 (95th percentile)[26] and we arbitrarily defined the upper limit as 50 reflux events per day.

The literature shows an extremely poor correlation between acid reflux measured with pHM and reflux

Table 4 Comparison of multichannel intraluminal impedance and pH monitoring

	pH monitoring positive	pH monitoring negative	Total
MII monitoring	27	17	44
positive MII monitoring negative	7	9	16
Total	34	26	60

Kappa = 0.147 (P = 0.223, 95%CI: 0.026-0.268). Overall percent agreement = 60%; MII: Multichannel intraluminal impedance.

episodes detected with scintigraphy. Although there are many studies reviewing the diagnostic methods, studies comparing GES and pHM, MII or MII-pHM are scarce.

Vandenplas *et al*^[37] compared the information provided by pHM and GES which were performed in 65 children investigated for suspected GERD. During a 1 h simultaneous recording period, 123 reflux episodes were recorded with both techniques but only six (4.9%) of them occurred simultaneously. Another study comparing results of scintigraphy and pHM showed that both methods concurrently detected only 42% reflux episodes^[38]. In our study, 142 (16.1%) of 880 reflux episodes were observed with both GES and MII/pHM. The reasons for this low concordance may be due to a few factors: (1) scintigraphy may show inadequate esophageal clearance or remnants or refluxes that cannot be shown with MII-pHM; (2) pH monitoring is not able to detect non acidic refluxes; (3) all reflux episodes may not propagate to at least 2 impedance channels; and (4) additionally, a frame acquisition technique may also affect the detection rate of GER events[17,37-39].

Studies found sensitivity and specificity for GES between 15%-59% and 83%-100%, respectively, when compared with 24-h esophageal pHM^[38,40-44]. In our study, the sensitivity of GES was higher than its specificity, in contrast to previous studies, and comparing the results of pHM and GES showed that two tests were in agreement for 29 (48.3%) patients and the kappa value was below zero. If pHM is considered as a reference test, PPA is 73.5% while NPA is 15.4%. For MII, 61.7% of patients had positive results for both MII and GES and the results seemed to be more comparable than pHM but the kappa value was not still significant. For MII-pHM, kappa was close to zero, overall percentage for agreement was 73.3% and, similar to the comparison with pHM and MII, PPA is much higher than NPA. These findings may be due to the fact that GES shows only postprandial reflux events and even 1 episode is accepted as a positive result. As there are no similar studies, we could not compare our results.

In an article evaluating 2178 studies^[45], 6 containing 408 participants were included and it was

Table 5 Sensitivity, specificity, positive and negative predictive values of diagnostic tests according to assumed gold standard test

Test	Gold standard							
	MII-pH monitoring			GES				
	Sensitivity, % (95%CI)	Specificity, % (95%CI)	PPV, % (95%CI)	NPV, % (95%CI)	Sensitivity, % (95%CI)	Specificity, % (95%CI)	PPV, % (95%CI)	NPV, % (95%CI)
MII-pHM	-	-	-	-	87.2 (73.6-94.7)	23.1 (6.2-54.0)	80.4 (66.5-89.7)	33.3 (9.0-69.1)
pHM alone	66.7 (52.0-78.9)	100 (62.9-100.0)	100 (87.4-100.0)	34.6 (17.9-55.6)	53.2 (38.2-67.6)	30.8 (10.4-61.1)	73.5 (55.3-86.5)	15.4 (5.0-35.7)
MII alone	73.3 (73.1-93.8)	100 (62.9-100.0)	100 (90.0-100.0)	56.3 (30.6-79.2)	72.3 (57.1-83.9)	23.1 (6.0-54.0)	77.3 (61.8-88.0)	18.6 (5.0-46.3)
GES	80.4 (66.5-89.7)	33.3 (9.0-69.1)	87.2 (73.6-94.7)	23.1 (6.1-54.0)	· -	-	-	-

GES: Gastroesophageal scintigraphy; MII-pHM: Multichannel intraluminal impedance-pH monitoring; pHM: Esophageal pH monitoring; MII: Multichannel intraluminal impedance monitoring; PPV: Positive predictive value; NPV: Negative predictive value.

concluded that the diagnostic accuracy of tests in children with suspected GERD is unclear. In these studies, the sensitivity of pHM ranged from 41-81%. pH monitoring can only detect acidic (pH < 4) episodes and underestimate postprandial refluxes which occurs in postprandial periods in most GER, particularly in infants^[39]. Shay et al^[46] evaluated 19 GERD patients with manometry, pHM and MII simultaneously for 2 h and found that only 19% of the refluxes could be detected by all three methods. In the MII study, more refluxes were detected comparing manometry and pHM (96% vs 76% and 28%, respectively) and 15% of refluxes were detected only by MII monitoring. In a study published in 2005^[47], 70 GER patients underwent various tests, including esophagogastroduodenoscopy with biopsy from the lower esophageal mucosa during the first visit, followed by an omeprazole challenge test (OCT), radionuclide scintigraphy, barium swallow and finally 24-h esophageal pHM. A positive concordance of three or more tests was taken as the gold standard. As a single diagnostic test, pHM had the best combination of sensitivity and specificity (77.7% and 92%), while the values for scintigraphy were 15.5% and 96%.

In our study, GERD was diagnosed in 34 (57.7%), 44 (73.3%), 47 (78.3%) and 51 (85%) patients by pHM, MII, GES and MII/pHM, respectively. pHM shows the lowest positive results and MII-pHM shows that 54.9% of refluxes were nonacidic so by pHM evaluation only, some patients should not have been diagnosed.

About 70% of reflux episodes occur during feeding and the first 2 postprandial hours and the remaining episodes occur during the remaining time before the next feeding [5]. This is especially important for patients with pulmonary symptoms as shown in some studies [48]. Dalby et a [49] stated that MII/pHM can detect all refluxes (acidic/nonacidic), content of the refluxes, association of symptoms and reflux episodes with high reproducibility. By the addition of MII in our study, the number of patients diagnosed as having

GERD increased by 50%.

Our results show that MII-pHM is more sensitive than both GES and pHM. When MII-pHM or GES is considered as the gold standard test, sensitivities of GES and MII-pHM are above 80%. However, the negative predictive value and NPA are low, ranging from 23.1% to 33.3%. This may be due to the fact that even reflux in one frame was accepted as a positive result. The clinical significance of the number of episodes and intensity of the reflux events has not been clearly documented. In one study, it was stated that an increasing episode number in GES might be a predictor for reflux-related symptom severity^[50].

Our results demonstrate that there is slight or no agreement between MII/pH monitoring and GES results. The compatibility is especially weaker for negative results. MII-pHM showed better results than other tests for sensitivity and positive predictivity.

We recognize that this study has limitations. The absence of asymptomatic control children limits our ability to infer any clinical relevance but for ethical reasons, we did not obtain a control study group. Also, normal values for children for MII-pH monitoring have not been established so the results have been compared with those described in a few studies and the results might have changed with different cutoff values. Patient selection may have an impact on the prevalence of GER in patients as we studied a heterogeneous group in age and symptoms, including both subjects with and without typical GER symptoms. It would be valuable to check if the test results were correlated with different patterns or severity of complaints, but it was not the aim of this study. Additionally, we did not accept one test as the gold standard. As far as we know, this is the first study to compare MII-pHM and GES.

In conclusion, the most sensitive test for diagnosing GERD is MII-pHM. No or slight agreement was found between pHM, MII, MII-pHM and GES for diagnosis of GERD. Scintigraphy should be interpreted

carefully and efforts should be aimed at developing new diagnostic standards for scintigraphy in GERD. One must keep in mind that negative results do not mean that the patient does not have GERD, while one reflux episode may represent a physiological postprandial reflux. Also, standardization and new diagnositic criteria need to be evaluated for scintigraphy. With the use of new techniques for diagnosis, some questions are answered but some new questions have arisen and the ideal diagnostic test for GERD has not been identified yet.

COMMENTS

Background

It is important to distinguish physiological gastroesophageal reflux (GER) events from GER disease (GERD). Currently, multichannel intraluminal impedance-pH monitoring (MII-pHM) is accepted as the gold standard for diagnosis of GERD but it is expensive and not commonly available and normal values for all age groups have not yet been established.

Research frontiers

Gastroesophageal reflux scintigraphy (GES) is easy to perform and more widely available worldwide than MII-pHM. Although there are many studies reviewing diagnostic methods, studies comparing GES and pHM, MII or MII-pHM are scarce.

Innovations and breakthroughs

This study evaluated the agreement of GES and MII-pH monitoring and showed a slight or no agreement between reflux measured with MII-pHM and reflux episodes detected with scintigraphy.

Applications

These results show that MII-pHM is more sensitive compared to GES. Scintigraphy should be interpreted carefully and efforts should be aimed at developing new diagnostic standards for scintigraphy in GERD.

Terminology

Impedance testing is based on changes in electrical resistance between two rings produced by the presence of bolus inside the esophageal lumen. Decrease in resistance indicates the presence of a liquid bolus. Impedance catheters have multiple sets of impedance-measuring rings and can assess bolus movement and direction. GES involves the oral administration of a radiopharmaceutical followed by scintiscanning of the stomach and esophagus to detect reflux events during the recording session.

Peer-review

In the manuscript, the authors present a very interesting and diligently performed study on gastroesophageal reflux, primarily comparing a pH- and impedance-detection dependant on a scintigraphic method in a prospective, comparative way, analysing patients with both methods, and comparing the results.

REFERENCES

Vandenplas Y, Rudolph CD, Di Lorenzo C, Hassall E, Liptak G, Mazur L, Sondheimer J, Staiano A, Thomson M, Veereman-Wauters G, Wenzl TG. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). J Pediatr Gastroenterol Nutr 2009; 49: 498-547 [PMID: 19745761 DOI: 10.1097/MPG.0b013e3181b7f563]

- Yellon RF, Goyal A. What is the best test for pediatric gastroesophageal reflux disease? *Laryngoscope* 2013; 123: 2925-2927 [PMID: 24114940 DOI: 10.1002/lary.23656]
- Vandenplas Y. Challenges in the diagnosis of gastroesophageal reflux disease in infants and children. Expert Opin Med Diagn 2013; 7: 289-298 [PMID: 23581607 DOI: 10.1517/17530059.2013 .789857]
- Mousa HM, Rosen R, Woodley FW, Orsi M, Armas D, Faure C, Fortunato J, O'connor J, Skaggs B, Nurko S. Esophageal impedance monitoring for gastroesophageal reflux. *J Pediatr Gastroenterol Nutr* 2011; 52: 129-139 [PMID: 21240010 DOI: 10.1097/MPG.0b013e3181ffde67]
- 5 Skopnik H, Silny J, Heiber O, Schulz J, Rau G, Heimann G. Gastroesophageal reflux in infants: evaluation of a new intraluminal impedance technique. *J Pediatr Gastroenterol Nutr* 1996; 23: 591-598 [PMID: 8985851]
- Wenzl TG, Moroder C, Trachterna M, Thomson M, Silny J, Heimann G, Skopnik H. Esophageal pH monitoring and impedance measurement: a comparison of two diagnostic tests for gastroesophageal reflux. J Pediatr Gastroenterol Nutr 2002; 34: 519-523 [PMID: 12050578]
- Rosen R, Lord C, Nurko S. The sensitivity of multichannel intraluminal impedance and the pH probe in the evaluation of gastroesophageal reflux in children. *Clin Gastroenterol Hepatol* 2006; 4: 167-172 [PMID: 16469676]
- Woodley FW, Mousa H. Acid gastroesophageal reflux reports in infants: a comparison of esophageal pH monitoring and multichannel intraluminal impedance measurements. *Dig Dis* Sci 2006; 51: 1910-1916 [PMID: 17053958 DOI: 10.1007/ s10620-006-9179-0]
- 9 Vandenplas Y, Salvatore S, Devreker T, Hauser B. Gastrooesophageal reflux disease: oesophageal impedance versus pH monitoring. Acta Paediatr 2007; 96: 956-962 [PMID: 17498193 DOI: 10.1111/j.1651-2227.2007.00306.x]
- Francavilla R, Magistà AM, Bucci N, Villirillo A, Boscarelli G, Mappa L, Leone G, Fico S, Castellaneta S, Indrio F, Lionetti E, Moramarco F, Cavallo L. Comparison of esophageal pH and multichannel intraluminal impedance testing in pediatric patients with suspected gastroesophageal reflux. *J Pediatr Gastroenterol Nutr* 2010; 50: 154-160 [PMID: 19680154 DOI: 10.1097/MPG.0b013e3181a4c1d8]
- 11 Loots CM, van Wijk MP, Blondeau K, Dalby K, Peeters L, Rosen R, Salvatore S, Wenzl TG, Vandenplas Y, Benninga MA, Omari TI. Interobserver and intraobserver variability in pHimpedance analysis between 10 experts and automated analysis. *J Pediatr* 2012; 160: 441-446.e1 [PMID: 21924738 DOI: 10.1016/ j.jpeds.2011.08.017]
- 12 Smits MJ, Loots CM, van Wijk MP, Bredenoord AJ, Benninga MA, Smout AJ. An expert panel-based study on recognition of gastro-esophageal reflux in difficult esophageal pH-impedance tracings. Neurogastroenterol Motil 2015; 27: 637-645 [PMID: 25756933 DOI: 10.1111/nmo.12536]
- Ciecierega T, Gordon BL, Aronova A, Crawford CV, Zarnegar R. More art than science: impedance analysis prone to interpretation error. *J Gastrointest Surg* 2015; 19: 987-992 [PMID: 25876531 DOI: 10.1007/s11605-015-2809-0]
- 14 Wenzl TG, Benninga MA, Loots CM, Salvatore S, Vandenplas Y. Indications, methodology, and interpretation of combined esophageal impedance-pH monitoring in children: ESPGHAN EURO-PIG standard protocol. *J Pediatr Gastroenterol Nutr* 2012; 55: 230-234 [PMID: 22711055 DOI: 10.1097/MPG.0b013e3182592b65]
- Tuncel M, Kıratlı PO, Aksoy T, Bozkurt MF. Gastroesophageal reflux scintigraphy: interpretation methods and inter-reader agreement. World J Pediatr 2011; 7: 245-249 [PMID: 21822991 DOI: 10.1007/s12519-011-0322-4]
- 6 Patra S, Singh V, Chandra J, Kumar P, Tripathi M. Diagnostic modalities for gastro-esophageal reflux in infantile wheezers. *J Trop Pediatr* 2011; 57: 99-103 [PMID: 20595328 DOI: 10.1093/tropei/fmq056]
- 7 Codreanu I, Chamroonrat W, Edwards K, Zhuang H. Effects of



- the frame acquisition rate on the sensitivity of gastro-oesophageal reflux scintigraphy. *Br J Radiol* 2013; **86**: 20130084 [PMID: 23520226 DOI: 10.1259/bjr.20130084]
- 18 Elbl B, Birkenfeld B, Walecka A, Szymanowicz J, Listewnik M, Gwardyś A, Urasiński T. Upper gastrointestinal tract scintigraphy and ultrasonography in diagnosis of gastroesophageal reflux in children. *Pol J Radiol* 2011; 76: 63-67 [PMID: 22802818]
- 19 Waseem S, Islam S, Kahn G, Moshiree B, Talley NJ. Spectrum of gastroparesis in children. *J Pediatr Gastroenterol Nutr* 2012; 55: 166-172 [PMID: 22314391 DOI: 10.1097/MPG.0b013e31824cf06e]
- 20 Ravelli AM, Panarotto MB, Verdoni L, Consolati V, Bolognini S. Pulmonary aspiration shown by scintigraphy in gastroesophageal reflux-related respiratory disease. *Chest* 2006; 130: 1520-1526 [PMID: 17099032 DOI: 10.1378/chest.130.5.1520]
- Argon M, Duygun U, Daglioz G, Omür O, Demir E, Aydogdu S. Relationship between gastric emptying and gastroesophageal reflux in infants and children. *Clin Nucl Med* 2006; 31: 262-265 [PMID: 16622332 DOI: 10.1097/01.rlu.0000210500.64440.76]
- 22 Falk GL, Beattie J, Ing A, Falk SE, Magee M, Burton L, Van der Wall H. Scintigraphy in laryngopharyngeal and gastroesophageal reflux disease: a definitive diagnostic test? World J Gastroenterol 2015; 21: 3619-3627 [PMID: 25834329 DOI: 10.3748/wjg.v21. i12.3619]
- 23 Strobel CT, Byrne WJ, Ament ME, Euler AR. Correlation of esophageal lengths in children with height: application to the Tuttle test without prior esophageal manometry. *J Pediatr* 1979; 94: 81-84 [PMID: 758430 DOI: 10.1016/S0022-3476(79)80361-3]
- Zerbib F, des Varannes SB, Roman S, Pouderoux P, Artigue F, Chaput U, Mion F, Caillol F, Verin E, Bommelaer G, Ducrotté P, Galmiche JP, Sifrim D. Normal values and day-to-day variability of 24-h ambulatory oesophageal impedance-pH monitoring in a Belgian-French cohort of healthy subjects. *Aliment Pharmacol Ther* 2005; 22: 1011-1021 [PMID: 16268977 DOI: 10.1111/j.1365-2036.2005.02677.x]
- Zerbib F, Roman S, Bruley Des Varannes S, Gourcerol G, Coffin B, Ropert A, Lepicard P, Mion F. Normal values of pharyngeal and esophageal 24-hour pH impedance in individuals on and off therapy and interobserver reproducibility. *Clin Gastroenterol Hepatol* 2013; 11: 366-372 [PMID: 23142603 DOI: 10.1016/j.cgh.2012.10.041]
- Zentilin P, Iiritano E, Dulbecco P, Bilardi C, Savarino E, De Conca S, Parodi A, Reglioni S, Vigneri S, Savarino V. Normal values of 24-h ambulatory intraluminal impedance combined with pH-metry in subjects eating a Mediterranean diet. *Dig Liver Dis* 2006; 38: 226-232 [PMID: 16480938 DOI: 10.1016/j.dld.2005.12.011]
- 27 Pilic D, Fröhlich T, Nöh F, Pappas A, Schmidt-Choudhury A, Köhler H, Skopnik H, Wenzl TG. Detection of gastroesophageal reflux in children using combined multichannel intraluminal impedance and pH measurement: data from the German Pediatric Impedance Group. *J Pediatr* 2011; 158: 650-654.e1 [PMID: 21035128 DOI: 10.1016/j.jpeds.2010.09.033]
- 28 Shay S, Tutuian R, Sifrim D, Vela M, Wise J, Balaji N, Zhang X, Adhami T, Murray J, Peters J, Castell D. Twenty-four hour ambulatory simultaneous impedance and pH monitoring: a multicenter report of normal values from 60 healthy volunteers. Am J Gastroenterol 2004; 99: 1037-1043 [PMID: 15180722 DOI: 10.1111/j.1572-0241.04172.x]
- 29 Peat J, Barton B. Medical Statistics. Massachusetts: Blackwell Sci Pub, 2007: 267-277
- 30 Morgan EH, Hill LD, Siemson JK, Chapman KW, Botseas D. Studies of intraluminal esophageal and gastric pressure and pH. Bull Mason Clin 1960; 14: 53-89 [PMID: 13772569]
- 31 Demeester TR, Johnson LF, Kent AH. Evaluation of current operations for the prevention of gastroesophageal reflux. *Ann Surg* 1974; 180: 511-525 [PMID: 4413307 DOI: 10.1097/00000658-197 410000-00016]
- 32 Faust H, Kapp F, Fridrich R. Clarification of cardial insufficiency. A clinical, radiological, endoscopic and nuclear medicine study.

- Schweiz Med Wochenschr 1973; 103: 1750-1752 [PMID: 4752578]
- Pezzuoli G, Zannini P, Maruotti RA, Voci C, Negri G, Baisi A. A microcomputer based interactive system for the recording and automatic analysis of esophageal pH-studies. *Int Surg* 1983; 68: 223-226 [PMID: 6689317]
- Gawron AJ, Hirano I. Advances in diagnostic testing for gastroesophageal reflux disease. World J Gastroenterol 2010; 16: 3750-3756 [PMID: 20698036 DOI: 10.3748/wjg.v16.i30.3750]
- Pilic D, Höfs C, Weitmann S, Nöh F, Fröhlich T, Skopnik H, Köhler H, Wenzl TG, Schmidt-Choudhury A. Inter- and intraobserver agreement in 24-hour combined multiple intraluminal impedance and pH measurement in children. J Pediatr Gastroenterol Nutr 2011; 53: 255-259 [PMID: 21865970 DOI: 10.1097/MPG.0b013e318216940e]
- 36 Johnson LF, Demeester TR. Twenty-four-hour pH monitoring of the distal esophagus. A quantitative measure of gastroesophageal reflux. Am J Gastroenterol 1974; 62: 325-332 [PMID: 4432845]
- 37 Vandenplas Y, Derde MP, Piepsz A. Evaluation of reflux episodes during simultaneous esophageal pH monitoring and gastroesophageal reflux scintigraphy in children. J Pediatr Gastroenterol Nutr 1992; 14: 256-260 [PMID: 1619528]
- Orenstein SR, Klein HA, Rosenthal MS. Scintigraphy versus pH probe for quantification of pediatric gastroesophageal reflux: a study using concurrent multiplexed data and acid feedings. *J Nucl Med* 1993; 34: 1228-1234 [PMID: 8326376]
- 39 Demir H, Ozen H, Koçak N, Saltik-Temizel IN, Gürakan F. Does simultaneous gastric and esophageal pH monitoring increase the diagnosis of gastroesophageal reflux disease? *Turk J Pediatr* 2005; 47: 14-16 [PMID: 15884623]
- 40 Seibert JJ, Byrne WJ, Euler AR, Latture T, Leach M, Campbell M. Gastroesophageal reflux--the acid test: scintigraphy or the pH probe? AJR Am J Roentgenol 1983; 140: 1087-1090 [PMID: 6602471 DOI: 10.2214/ajr.140.6.1087]
- 41 Balson BM, Kravitz EK, McGeady SJ. Diagnosis and treatment of gastroesophageal reflux in children and adolescents with severe asthma. *Ann Allergy Asthma Immunol* 1998; 81: 159-164 [PMID: 9723562 DOI: 10.1016/S1081-1206(10)62803-7]
- 42 Arasu TS, Wyllie R, Fitzgerald JF, Franken EA, Siddiqui AR, Lehman GA, Eigen H, Grosfeld JL. Gastroesophageal reflux in infants and children comparative accuracy of diagnostic methods. J Pediatr 1980; 96: 798-803 [PMID: 7365577]
- 43 Tolia V, Kauffman RE. Comparison of evaluation of gastroesophageal reflux in infants using different feedings during intraesophageal pH monitoring. *J Pediatr Gastroenterol Nutr* 1990; 10: 426-429 [PMID: 2358973]
- 44 Peter CS, Sprodowski N, Bohnhorst B, Silny J, Poets CF. Gastroesophageal reflux and apnea of prematurity: no temporal relationship. *Pediatrics* 2002; 109: 8-11 [PMID: 11773535]
- 45 van der Pol RJ, Smits MJ, Venmans L, Boluyt N, Benninga MA, Tabbers MM. Diagnostic accuracy of tests in pediatric gastroesophageal reflux disease. *J Pediatr* 2013; 162: 983-7. e1-983-7.e4 [PMID: 23219449 DOI: 10.1016/j.jpeds.2012.10.041]
- 46 Shay S, Richter J. Direct comparison of impedance, manometry, and pH Probe in detecting reflux before and after a meal. *Dig Dis Sci* 2005; 50: 1584-1590 [PMID: 16133955 DOI: 10.1007/s10620-005-2901-5]
- 47 Madan K, Ahuja V, Gupta SD, Bal C, Kapoor A, Sharma MP. Impact of 24-h esophageal pH monitoring on the diagnosis of gastroesophageal reflux disease: defining the gold standard. *J Gastroenterol Hepatol* 2005; 20: 30-37 [PMID: 15610443 DOI: 10.1111/j.1440-1746.2004.03530.x]
- 48 Rosen R, Nurko S. The importance of multichannel intraluminal impedance in the evaluation of children with persistent respiratory symptoms. *Am J Gastroenterol* 2004; 99: 2452-2458 [PMID: 15571595 DOI: 10.1111/j.1572-0241.2004.40268.x]
- 49 Dalby K, Nielsen RG, Markoew S, Kruse-Andersen S, Husby S. Reproducibility of 24-hour combined multiple intraluminal impedance (MII) and pH measurements in infants and children.



- Evaluation of a diagnostic procedure for gastroesophageal reflux disease. *Dig Dis Sci* 2007; **52**: 2159-2165 [PMID: 17436090 DOI: 10.1007/s10620-006-9731-y]
- 50 Bingol Boz A, Aydn F, Celmeli F, Boz A, Artan R, Gungor
- F. Does gastroesophageal reflux scintigraphy correlate with clinical findings in children with chronic cough? *Nucl Med Commun* 2009; **30**: 802-806 [PMID: 19654561 DOI: 10.1097/MNM.0b013e32832fa27e]

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