

ORIGINAL PAPERS

Esophageal multichannel intraluminal impedance and pH-testing in the study of apparent life threatening episode incidents in infants

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ABSTRACT

Introduction: The conventional 24-hour pH monitoring is the gold standard for the diagnosis of gastro-esophageal reflux (GER), a possible cause of Apparent Life Threatening Episodes (ALTE). However, multichannel intraluminal impedance (MII) may provide advantages.

Objectives: Comparison of the results of MII and pH monitoring in patients undergoing MII-pH monitoring in the 3-year study period because of having suffered from ALTE.

Material and methods: Prospective study of MII-pH monitoring performed in our unit to infants < 12 months of age admitted for ALTE for a 3-year period.

Results: Thirty nine patients studied. 2,692 pH monitoring episodes, with median of 24 (IQ: 15-44) episodes/patient, 1.30 (IQ: 0.80-2.60) reflux/hour, 1 (IQ: 0-4) reflux episode > 5 min per patient and clearance of 1.20 (IQ: 0.70-2.20) min/reflux. With pH monitoring analysis, 14 children (35.9 %) could have been diagnosed as GER (8 mild, 4 moderate and 2 severe) based on the classical criteria. MII identified a total of 8,895 events; only 3,219 among them were refluxes, with a median of 75 (IQ: 54-111) per patient, 1.30 (IQ: 1.3-2.6) episodes/hour. With MII-pH monitoring combination there were 21.60 (SD 15.21) acid reflux episodes, 67.33 weekly acid (SD 32.09) and 3.34 (SD 7.23) non-acid, being finally diagnosed 33 patients as GER.

Conclusions: The association of pH monitoring and MII provides additional information that improves GER diagnostic performance without posing any additional risk to the infant patient. The non-acid/weekly acid refluxes, not detected by pH monitoring, account for a high percentage of episodes, this may have diagnostic and therapeutic significance, especially in infants. Further studies are needed to assess the normality of MMI in pediatric patients.

Key words: Esophageal impedance. pH-testing. Gastroesophageal reflux. Childhood.

INTRODUCTION

Acids during gastro-esophageal reflux (GER) have been considered the main cause for gastro-esophageal reflux disease (GERD) in infants (1), a disease which manifests with digestive and extra-gastrointestinal symptoms such as apnea and apparent life threatening episodes (ALTE) (2). ALTE is described as an impromptu and unexpected episode exhibiting to the scared observer symptoms of imminent or true death requiring intervention by the caregiver such as: apnea, changes in skin color (cyanosis, ruddy or pale) and/or changes in muscle tone. Recurrent regurgitation occurs in 60-70 % of the patients, whom show abnormal esophageal pH measurements in 40-60 % of the cases. The relationship between GER and obstructive or mixed apnea is more convincing during waking hours, in the supine position or within an hour of having been fed. Various techniques have been used to categorize reflux, allowing us to measure and assess the underlying problem –the exposition time of the esophagus to gastric juices. Additionally, it is of interest to determine if symptoms correlate with those episodes during which there is exposure to gastric juices (3).

Due to its similarities to apnea of prematurity (4), those infants whom have presented ALTE belong to a heterogeneous group representing multiple pathologies, half of which are generally diagnosed with an underlying pathology where GER is one of the main causes (5). Recent studies have shown that, in spite of a decline in instances

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of sudden infant death syndrome (SIDS), primarily due to the reduction in popularity of placing the infant in the prone position to sleep, the frequency of hospital admissions for ALTE have remained the same (6). There also remains a group of infants classified under "without identifiable cause" whom have the highest tendency for sudden death, oscillating between 0.5 % and 7 % according to different authors (6,7). However, it is conceivable that there should be a cause for all infants presenting ALTE, even if sometimes we cannot define it. In consideration of this, a comprehensive study of this group of infants is necessary with the goal of ruling out GER as the etiology. So we ask ourselves, if combining pH-testing with MII would possibly improve upon the proficiency of the diagnoses. The appearance of an ALTE is associated with GER in around 20 % of the cases.

Between 2000 and 2005, the annual incidence for diagnosing GERD in infants less than one year old has tripled (3.4 % to 12.3 %). This implies that research is necessary to put a value on the relationship between MII and pH-testing in this age group (8).

pH-testing over a 24 hour period has been defined as the gold standard diagnosis for GER (9). But, diverse studies show that a large number of infants admitted to the emergency room for ALTE have alterations in at least one parameter of the pH-test (10), which, however, could lead us to over-diagnose GER as the principle cause (11).

Multichannel intraluminal impedance (MII)-pH-testing could prove advantageous in the detection of acid reflux and non-acid reflux, the clearing times for these and the progression distances up the esophagus. It is a method with a potential for high sensitivity in detecting all types of reflux episodes. It permits the detection of any retrograde flux of stomach juices and distinguishes them from swallowing. Reflux is best detected by impedance and its acidity is best determined by pH-testing. In the same way, the combination of pH-testing and MII uses its individual channels to help characterize refluxed materials (liquids, gases and mixed) and the distance that the bolus travels in the esophagus.

OBJECTIVES

The objective of this work is a description of the epidemiological and clinical data from infants admitted for ALTE and subjected to MII-pH-testing over the study period and the comparison of those results obtained via these two methods determining the sensitivity and the specificity of each one.

PATIENTS AND METHODS

A retrospective study was done for MII-pH-testing between September 2008 and December 2011 on infants less

than one year old admitted under our care on the hospital floor for having presented an apparent life threatening disorder.

The Monitor Ambulatorio Ohmega® (Medical Measurement Systems) was used. The software used incorporated automatic analysis of the entries and easy-to-read and easy-to-interpret readouts. The analysis of the data obtained by the equipment can be analyzed in agreement with the criteria and point system of Demeester and Boix-Ochoa. Disposable monocrystalline antimony catheters with 6 channels for measuring impedance and one channel for measuring pH were used. The location of the electrode tip was determined using the Strobel formula ($0.252 \times \text{length (cm)} + 5$) and then confirmed using fluoroscopy to position it at the level of the T7-T8 vertebrae (about 2 cm from the diaphragm). Informed consent was obtained in all case studies. All of the studies were made in the hospital setting. The patient's caregiver remained present for the 24 hours of measurement taking and was given a paper where they registered feeding and sleeping times and the times of appearance of any symptoms considered abnormal (coughing, vomiting, crying...). No patients had previously received either antacids or prokinetic treatments. All of the MII-pH-test results were originally reported by one of the three hospital unit doctors on staff and then passed on for reinterpretation by a single researcher.

Given that pH-testing is considered to be the golden standard for defining the GER pathology, the parameters considered from the start to be labeled as "classic" include the following: The number of reflux episodes (NR), the number of reflux episodes longer than 5 minutes ($\text{NR} > 5$), the number of reflux episodes of longer duration ($\text{DR} + \text{L}$), the fraction of time during which the pH is lower than 4 or the reflux index (IR). To analyze the test results for the infants, normal standards published by Boix-Ochoa (12) were used. Other parameters were also considered: the average length of time of a reflux episode (DMR), the average length of time of reflux during sleep (DMRS), the number of refluxes per hour (NR/h), the average time for pH recovery or esophagus clearing (Acl. E), alkaline reflux (RA), the area under the curve for $\text{pH} < 4$ ($\text{AC} < 4$) and the oscillatory index (IO).

Subsequently, a positive or negative GER diagnosis was established based on the results given by impedance measurement analysis as compared with the diagnostic results from pH-testing. For this, the following parameters were taken into account: a MII reflux (a drop in impedance, retrograde, greater than 50 % from the base line and in at least two of the more distal channels); an acid reflux (reflux episodes associated with a pH less than 4); an alkaline reflux (reflux episodes associated with a pH greater than 7); and the reflux index (the number of refluxes per hour, considered pathological at values exceeding 4 %). Published normal standards for older youth and young adults (13,14) were used in interpreting the MII results, since at this time there are no available equivalents for infants.

Based on clinical evolution on the hospital floor and all the complementary tests executed (echocardiography, ultrasonography of the cranium, digestive tract X-rays and/or abdominal ultrasonography and MII-pH-testing), a final diagnosis was determined for each case: a) No GER or a physiological, non-clinical case; and b) presence of a GER pathology as the probable cause of ALTE.

Quantitative variables were expressed in form of the mean \pm the standard deviation and the qualitative variables were expressed as percentages. For the study of statistical associations a simple or bivariate analysis was used. The Shapiro-Wilk test was used to determine the normality of the distribution. The Student's t test and chi-squared test were used to compare the parametrical variables. The Mann-Whitney-Wilcoxon or McNemar tests were used as non-parametrical tests. The correlation between these variables was analyzed using Spearman tests and their relation to each other using Cramer's V and the phi coefficient. A value of p less than 0.05 was considered significant.

RESULTS

Thirty nine patients were evaluated over this 3 year period. A total of 25/39 were boys (64.1 %). The average age

was 3.52 months old (IQ: 1.22-4.80). The average weight and length were 4.66 kg (IQ: 3.30-5.42) and 55 cm (IQ: 51-60). The average length of testing was 20.73 (DE 2.88) hours.

pH-testing registered 2692 refluxes (Table I), with an average of 14 (IQ: 15-44) refluxes/patient, a reflux index or acid expression of 1.30 (IQ: 0.80-2.60) refluxes/hour, 1 reflux episode longer than 5 min per patient and an average clearance time in the esophagus of 1.20 (IQ: 0.70-2.20) min/reflux. From pH-testing alone, 14 infants (35.9 %) would have been diagnosed with GER (8 mild, 4 moderate and 2 acute) using the established "classic" criteria cited in the contributing material and methods.

Using MII, a total of 8,895 events were registered (Table I), of which only 3219 were reflux. There was an average of 75 (IQ: 54-111) refluxes per patient at a rate of 1.30 (IQ: 1.3-2.6) episodes/hour. Seventy-three point sixty seven percent (with a confidence interval of 95 % between 56.76 % and 85.82 %) of the refluxes reached the level of the central electrode (Z3) located 6 cm from the tip of the electrode and corresponding with the middle of the esophagus for the patients of this age. Here the time for the esophagus to clear was 4.2 min/reflux (IQ: 2.40-5.20), as compared to 9.20 min (IQ: 7.1-10.4) in the most distal electrode (Z6) and have statistically sig-

Table I. Comparison of the results for pH-testing and MII-pH-testing variables

	pH-testing		MII-pH-testing		p
<i>n</i>	39				
Total number of GER episodes	2,692		3,219		0.001
Reflux index (refluxes/hour)	1.3 (IQ: 0.8-2.6)		1.3 (IQ: 1.3-2.6)		ns
GER > 5 min	1 (IQ: 0-4)		-		-
Chemical clearing time (min/reflux)	1,2 (IQ: 0.7-2.2)		-		-
Bolus clearing time (min/reflux)	-		Z3	4,2 (IQ: 2.4-5.2)	0.0001
			Z6	9,2 (IQ: 7.1-10.4)	
GER diagnosis	Mild	8			0.0001
	Moderate	4	33		
	Acute	2			
Average number of refluxes/patient	24 (IQ: 15-44)		75 (IQ: 54-111)		0.0001
Acidic GER episodes	24 (IQ: 15-44)		17 (IQ: 9-24)		ns
NON-acidic GER episodes	-		58 (IQ: 42-85)		-
Progression of reflux	1 level (pH1)		6 levels (Z1 a Z6)		-

nificant differences (p 0.001). Using MII-pH-testing, the average amount of acid refluxes per patient were 21.60 (DE 15.21), mildly acidic refluxes were 67.33 (DE 32.09) and non-acidic refluxes were 3.34 (DE 7.23). Thirty-three patients were diagnosed with GER.

The analyzed parameters for MII-pH-testing are listed in table I. The percentage of GER episodes detected with pH-testing (2,692) was 83.6 % of those detected by MII (3,219), showing a statistically significant difference (p 0.001). Likewise, if we only take into account test results without putting any worth upon clinical values, the number of patients diagnosed with reflux using MII-pH-testing (33) is greater, with a statistical significance of p < 0.0001, than the number diagnosed using only conventional pH-testing (14).

To compare MII with the theoretical gold standard for diagnosing GER (pH-testing), our data series (Table II) shows a sensibility of 100 %, a specificity of 25 %, a VPP of 55.9 % and a VPN of 100 %, without demonstrating any statistically significant relationship with the final true diagnosis.

After the clinical data was taken and the complementary tests were done on each patient, we have a total of 18 cases which were finally diagnosed with gastroesophageal reflux as the main cause for ALTE (Table III). Taking into account this final result, pH-testing in our data series has a sensibility of 63.2 % with a specificity of 90 %, a positive predictive value (VPP) of 85.7 % and a negative predictive value (VPN) of 72 %. There is a statistically-significant relationship when applying the chi-squared test (p 0.001) and contingency coefficients Phi and Cramer's V of 0.55 (p 0.001).

If we take into account the cut points used in our work for defining the presence of GER using pH-testing (Boix-Ochoa > 11.99) and for MII-pH-testing results (as estimated from values for young adults, for lack of control values), we compare them with the real diagnosis of pathological GER and we analyze the ROC curves. Based on the area under the curve, values can be interpreted giving 0.766 for pH-testing and 0.599 for MII.

DISCUSSION

Around 70-85 % of infants less than 2 months old have episodes of regurgitation; but in 95 % of these cases, they are resolved without further intervention before one year of age (15). In a non-negligible percent of cases, extra-gastrointestinal symptoms manifest themselves, among which ALTE stands out (around 20 % of these are due to GER). However it is possible that occurrences in small infants could remain undiagnosed as pH-testing is pathologic in 80 % of the cases, requiring a reflux event coinciding with the clinical episode during the testing hours to confirm a correlation between GER and ALTE (16).

The relation between MII and pH-testing, in addition to providing data about non-acid refluxes, non-liquid refluxes and the distance traveled by the bolus, gives information about improving the efficiency of the diagnosis without submitting the patient to any additional risks. Nevertheless, there is no forecasted published research to determine if the related diagnosis, particularly with non-acid reflux, changes the prognosis or influences the type of therapy to be used in these patients.

It is still necessary to define a value for normal standards in MII on pediatric patients. There exist published values for premature infants (17) and adults (18,19). Additionally the reproducibility of the MII-pH-testing data is relatively poor in children (20). The researcher is required to dedicate, on average, somewhere between 30 minutes and 4 hours (21) for the interpretation of results for this test.

There is a high percentage of non-acidic and mildly-acidic refluxes, which are not detectable using pH-testing. This could be of diagnostic importance, especially in infants presenting clinical extra-gastrointestinal symptoms (apnea ...) and having a tamponade of gastric contents due to the frequent ingestion of lactic foods (22). The combination of MII with monitoring using pH-testing allows for diagnosing the existence of alkaline reflux and moderately-acidic refluxes, thus improving upon this limitation presented in the field of conventional pH-testing.

Table II. Contingent GER diagnoses using each one of the two techniques (revising the gold standard)

	<i>GER diagnosis using pH-testing</i>	<i>No GER diagnosis using pH-testing</i>	
<i>GER diagnosis using MII</i>	14	19	33
<i>No GER diagnosis using MII</i>	0	6	6
	14	25	39

Table III. The final diagnoses of ALTE caused by GER (GERD) and the diagnoses of GER using each esophageal technique

	<i>GERD diagnosis n = 18</i>	<i>No GERD diagnosis n = 21</i>
<i>GER diagnosis using pH-testing</i>	12	2
<i>GER diagnosis using MII</i>	18	15

In our data, the number of non-acid refluxes was 77.3 % of reflux episodes, a number very similar to that published by Rosen et al. (23).

The effectiveness of the diagnosis, therefore, improves when combining the two techniques. Thus, it is possible to complete the study of GER, thereby permitting the classification of acidic or non-acidic episodes (an average of 58 mildly-acidic or non-acidic refluxes were detected per patient), defining the relationship between atypical symptoms and each type of episode, characterizing the type of material refluxed in liquid, gas or mixed form, and determining the ascension height and the clearing time (12,13), much greater in the middle and lower thirds than is detectable with pH-testing (this is evident in table I and justified by the possibility that the bolus persists in the esophagus but with a progressive increase in pH).

It was finally determined not to give GER as a pathological diagnosis to patients for whom the MII assigned a certain grade of GER, considering that the specificity of MII with respect to the final diagnosis (the relationship of GER catalogued by esophageal probe during such clinical episodes as those compatible with the motive for admission) is less than (28 %) that of pH-testing (90 %), giving a high sensibility (100 %) and a much higher VPN (100 % instead of 76 %). The ROC curves show a greater area under the curve (AUC) for pH-testing than for MII due to its low specificity.

On the other hand, it is seen that pH-testing shows a greater average for acidic refluxes per patient than MII, which could be explained by a small percentile of acid reflux events manifesting themselves as slow drops in pH undetectable by impedance. This suggests that the combination of both techniques is better than MII or pH-testing alone.

Our research presents its own limitations both because the number of patients in the study is not very high and due to the inevitable subjectivity to interpretation of MII-pH-testing in infants without having clear normal standards for this age group.

In summary, MII supports the GER diagnosis made by pH-testing, now that it doesn't always give altered results (24) indicative of non-acidic GER in infants. However, this is all very tentative due to the lack of normal standards for this age group when using MII. The combination of both techniques permits the detection of all reflux events and offers the best possible evaluation of the functionality of the anti-reflux barrier. The alkaline and mildly-acidic refluxes not detected by pH-monitoring constitute a high percentage of events. This could be of diagnostic and therapeutic importance (25), especially in younger infants at risk of esophageal disease not associated with acids.

Studies are still necessary to evaluate the normal standards for MII in pediatric patients. The results of our work confirm that MII-pH-testing is an essential technique for the diagnosis of GER in the case of infants admitted for ALTE.

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