

Disagreement between symptom-reflux association analysis parameters in pediatric gastroesophageal reflux disease investigation

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Abstract

AIM: To assess the agreement within 3 commonly used symptom-reflux association analysis (SAA) parameters investigating gastroesophageal reflux disease (GERD) in infants.

METHODS: Twenty three infants with suspected GERD were included in this study. Symptom index (SI), Symptom sensitivity index (SSI) and symptom association probability (SAP) related to cough and irritability were calculated after 24 h combined pH/multiple intraluminal impedance (MII) monitoring. Through defined cut-off values, SI, SSI and SAP values are differentiated in normal and abnormal, whereas abnormal values point towards gastroesophageal reflux (GER) as the origin of symptoms. We analyzed the correlation and the concordance of the diagnostic classification of these 3 SAA parameters.

RESULTS: Evaluating the GER-irritability association, SI, SSI and SAP showed non-identical classification of normal and abnormal cases in 39.2% of the infants. When irritability was taken as a symptom, there was only a poor inter-parameter association between SI and SSI, and between SI and SAP (Kendall's tau $b = 0.37$, $P < 0.05$; Kendall's tau $b = 0.36$, $P < 0.05$, respectively). Evaluating the GER-cough association, SI, SSI and SAP showed non-identical classification of normal and abnormal cases in 52.2% of the patients. When cough was taken as a symptom, only SI and SSI showed a poor inter-parameter association (Kendall's tau $b = 0.33$, $P < 0.05$).

CONCLUSION: In infants investigated for suspected GERD with pH/MII-monitoring, SI, SSI and SAP showed a poor inter-parameter association and important disagreements in diagnostic classification. These limitations must be taken into consideration when interpreting the results of SAA in infants.

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Key words: Gastroesophageal reflux disease; Infant; Symptom-reflux association analysis; Intraluminal impedance monitoring; pH

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INTRODUCTION

Gastroesophageal reflux disease (GERD) remains one of the most common diagnoses made by pediatric gastroenterologists. By definition, gastroesophageal reflux (GER) is the involuntary passage of gastric contents into the esophagus or oropharynx, which is a physiological process that appears in every individual particularly after meals^[1]. When GER causes troublesome symptoms and/or complications, it is referred to as GERD^[2]. Clinical manifestations in infants include among others regurgitation, vomiting, irritability and cough^[1]. A main problem in the diagnosis of GERD is the association of symptoms with GER, especially the non-specific ones. While endoscopy can detect GER complications such as mucosal inflammation, symptom-reflux association analysis (SAA) is the only available method that can adequately identify GER as the cause of short lived symptoms^[3].

SAA aims to show and quantify a temporal relation between symptoms and GER. With qualification, a significant temporal relation between symptoms and GER, thus an abnormal result of the SAA parameter, may suggest GERD. Three parameters are often used to address this temporal relationship: Symptom index (SI), symptom sensitivity index (SSI) and symptom association probability (SAP)^[3-6]. A pre-condition required for SAA is a technical measure that identifies GER episodes in the individual esophagus. Two methods can be used: pH-monitoring and a combined pH/multiple intraluminal impedance (MII) monitoring.

In infants, GERD occurs frequently during the first months of life. During this period GER is often non-acid, because the frequent milk intake acts as a potent buffer of gastric acidity. pH-monitoring alone has the disadvantage of only detecting acid GER. The newer MII technique to measure GER allows the additional detection of non-acid GER and thus more GER events. This is the main difference from pH-measurement alone. It is likely that a combined pH/MII measurement will replace single pH-measurement in the future^[4,7,8].

Defined cut-off values of the SAA parameters help to decide whether symptom episodes which occurred during GER monitoring are related to GER or not. Despite routine clinical use in pediatrics^[6], SAA parameters have never been validated in children or in infants. The problem is the lack of an objective and reliable gold standard to which these parameters can be compared, as well as the ethical difficulty posed by obtaining data from healthy children. The correlation of these 3 parameters as well as the concordance of abnormal results within these parameters in infants is unknown. Therefore, a comparison between studies using different SAA parameters is not possible. Additional questions arise as to whether only one SAA parameter could be a substitute for the others or how to interpret different results of the various SAA parameters measured in one individual.

Condino *et al*^[5] reported that in infants hospitalized for evaluation of GER, fussiness/pain and cough were the most frequent symptoms and were found to be the most

frequent symptoms related to GER detected by combined pH/MII monitoring. We assessed SI, SSI and SAP for irritability and cough in a group of infants who underwent combined pH/MII monitoring for suspected GERD. In order to evaluate the agreement between these 3 parameters we analyzed the correlation and the concordance between them in normal and abnormal classification.

MATERIALS AND METHODS

In this retrospective study, combined pH/MII tracings of consecutively investigated infants performed between October 2006 and January 2009 were reviewed. All infants included had irritability and cough among other GER-like symptoms and underwent 24 h combined pH/MII monitoring for suspicion of GERD. Patients were clinically evaluated prior to combined pH/MII analysis. Various investigations such as barium swallow, esophagogastroduodenoscopy and laboratory analysis were performed based on history and clinical signs. A barium swallow was performed in infants with suspected anatomic upper gastrointestinal anomalies. Esophagogastroduodenoscopy was performed in the case of GERD resistant to therapy and to detect eosinophilic esophagitis. Diagnosis of esophagitis was based on histology of esophageal biopsies^[9]. Therapy was prescribed by the referring physicians or by one of the authors (P.B.). Therapy was not discontinued during the entire observation period.

Twenty four h combined pH/MII measurement was performed using hardware and software by Sandhill Technologies (Sandhill Scientific Inc., Highlands Ranch, CO, USA). A single-use catheter (ConforTEC[®] pH-MII probe ZIN-BS 45) with a diameter of 2.13 mm was placed transnasally. This probe consisted of six 1.5 cm impedance recording segments and one pH-electrode, located within the distal impedance segment. The middle of each impedance segment was located at 0, 1.5, 3, 4.5, 6 and 7.5 cm above the pH-electrode. The initial positioning of the catheter was estimated using the following formula: $(0.156 \times \text{height in cm}) + 6.88 \text{ cm} = \text{length of pH-electrode from nose to distal esophagus}$ ^[10]. Proper positioning of each catheter was confirmed by X-ray. The pH-electrode was placed 2 vertebral bodies above the diaphragm with a tolerance margin of 5 mm. The probe was connected to the portable recording device. An external reference electrode was attached posteriorly to the patient's chest.

The studies were performed on an inpatient basis. The caregivers (nurse and parents) were properly instructed by the attending physician on how to register the irritability and cough events on the portable recording device. We defined the term "irritability" as crying or whining. A child was irritable either if it cried or if it showed behavior of being unwell, expressed as making a grimace on the verge of crying. The latter was the perception of the parents. The pH/MII tracings were evaluated using the BioVIEW analysis software (Sandhill Scientific, Inc.) and each study was manually reviewed by a pediatric gastroenterologist. Patients with less than 20 h of recording were excluded from the study. A (liquid) GER episode detected by im-

pedance was defined as a retrograde drop in impedance by more than 50% of baseline in the distal 2 channels^[11]. Gas only episodes were not included in the analysis. A symptom was considered related to a GER event if it occurred within a 5 min window from the GER event^[12,13].

The SI was defined as the number of GER-related symptoms divided by the total number of symptoms, reflecting the percentage of symptoms related to GER episodes^[12]. The SSI was defined as the number of GER-related symptoms divided by the total number of GER episodes, reflecting the percentage of GER associated with symptoms^[14]. SAP was defined as the likelihood that the patients' symptoms were related to GER based on a statistical analysis (cross tabulation) of a contingency table consisting of 4 possible combinations of GER and symptoms. The SAP was calculated as $(1-P) \times 100\%$, with the *P*-value calculated using Fisher's exact test^[15]. The SAP calculation was provided in the software package of the pH/MII monitoring device. Based on the literature, SI values of $\geq 50\%$, SSI values of $\geq 10\%$ and SAP values of $\geq 95\%$ were considered abnormal^[3,5,6].

Statistical analysis

Statistical analysis was performed with SAS 9.2 (The SAS Institute, Cary, NC, USA). Continuous variables are presented as median and interquartile range (IQR) or, if an approximately normal distribution was assumed, as mean \pm SD. *P*-values < 0.05 were considered significant. Concordance between the different SAA methods was assessed by Kendall's tau-b. Kendall's tau-b calculates a measure of concordance based on the number of concordant and discordant pairs and uses a correction for tied pairs. It ranges between -1 and +1, where +1 is perfect concordance and -1 perfect discordance. A value of zero indicates the absence of any concordance. In the case of continuous variables, rankings were compared^[16].

The study was approved by the local ethics committee of the University of Fribourg, Switzerland.

RESULTS

Patient characteristics

Twenty-three infants aged 2 wk to 11 mo (median 3 mo, IQR 2.8 mo) were included in this study. 19 patients were male. One patient was under ranitidine treatment, 4 patients were under sucalfate treatment, 3 patients were under omeprazole treatment and 7 patients had thickened feeding. Mean duration of the procedure was 22 h and 44 min \pm 1 h 11 min. A previous barium meal was performed in 11 patients and showed a hiatus hernia in 1 case. Two patients had undergone esophagogastroduodenoscopy and biopsies after combined pH/MII monitoring, which showed esophagitis in both.

A total of 1692 GER episodes were detected, 395 were acid (23%) and 1297 non-acid (77%). 421 irritability episodes were reported, 165 (39%) were related to GER. There were 155 cough episodes, 73 (47%) related to GER. Table 1 summarizes the characteristics of the registered GER and symptom episodes.

Table 1 Characteristics of the registered reflux and symptom episodes

	GER episodes	Irritability episodes	Cough episodes
Min	22	2	1
Max	141	82	19
Median	67	11	5
IQR	48	18	10
Sum	1692	421	155

GER: Gastroesophageal reflux; Min: Minimal number for a single patient; Max: Maximal number for a single patient; Median: Median value for all patients; IQR: Interquartile range.

Symptom-reflux association analysis

We investigated the GER-irritability association and found the following overall values: SI 25%, IQR 37.5%; SSI 4.5%, IQR 8.1%; and SAP 54%, IQR 78%. Additionally, we investigated the GER-cough association and found the following overall values: SI 50%, IQR 75%; SSI 3.6%, IQR 4.3%; and SAP 38.4% \pm 43.3%. Abnormal results for the GER-irritability association were found for 8 patients in SI (34.8%), for 5 patients in SSI (21.7%), and 3 patients in SAP (13.0%). We found abnormal results for the GER-cough association in 13 patients for SI (56.5%), 2 patients for SSI (8.7%), and in 1 patient for SAP (4.3%). Evaluation of the diagnostic classification in normal and abnormal cases for the GER-irritability association showed 60.8% of the patients with identical classification, and 39.2% with non-identical classification. Evaluation of the diagnostic classification in normal and abnormal cases for the GER-cough association showed 47.8% of the patients with identical classification, and 52.2% with non-identical classification. Table 2 summarizes the data obtained.

All SAA parameters for the GER-irritability association were positive in one infant. This infant showed a notable GER on barium swallow without an anatomic anomaly. One infant had 3 positive SAA parameters for the GER-cough association. This infant had chronic esophagitis on esophagogastroduodenoscopy.

Evaluation of the diagnostic classification between the GER-irritability SAA parameters showed the following values: SI and SSI Kendall's tau $b = 0.2791$, $P = 0.2153$; SI and SAP Kendall's tau $b = 0.2593$, $P = 0.2748$; SSI and SAP Kendall's tau $b = 0.4219$, $P = 0.1618$. Evaluation of the diagnostic classification between the GER-cough SAA parameters showed the following values: SI and SSI Kendall's tau $b = 0.2707$, $P = 0.1255$; SI and SAP Kendall's tau $b = 0.1870$, $P = 0.2987$; SSI and SAP Kendall's tau $b = 0.6908$, $P = 0.2847$.

We found a poor correlation between the parameters SI and SSI in both symptom categories, irritability and cough. We also found a poor correlation between SI and SAP for the irritability symptom category (Table 3).

DISCUSSION

We investigated the agreement of different SAA parameters in infants who underwent combined pH/MII moni-

Table 2 Categorization of SI, SSI and SAP

SI	SSI	SAP	Number of infants	Percent	Cumulative frequency	Cumulative percent
Irritability/reflux association						
Abnormal	Abnormal	Abnormal	1	4.35	1	4.35
Abnormal	Abnormal	Normal	2	8.70	3	13.04
Abnormal	Normal	Abnormal	1	4.35	4	17.39
Abnormal	Normal	Normal	4	17.39	8	34.78
Normal	Abnormal	Abnormal	1	4.35	9	39.13
Normal	Abnormal	Normal	1	4.35	10	43.48
Normal	Normal	Normal	13	56.52	23	100.00
Cough/reflux association						
Abnormal	Abnormal	Abnormal	1	4.35	1	4.35
Abnormal	Abnormal	Normal	1	4.35	2	8.70
Abnormal	Normal	Normal	11	47.83	13	56.52
Normal	Normal	Normal	10	43.48	23	100.00

SI: Symptom index, abnormal if SI \geq 50%; SSI: Symptom sensitivity index, abnormal if SSI \geq 10%; SAP: Symptom association probability, abnormal if SAP \geq 95%.

Table 3 Correlations between SI, SSI and SAP for the irritability/reflux association and the cough/reflux association expressed in Kendall's tau b

	Irritability			Cough		
	SI	SSI	SAP	SI	SSI	SAP
SI	-	0.37102 ($P = 0.0147$)	0.36011 ($P = 0.0225$)	-	0.32725 ($P = 0.0362$)	0.20959 ($P = 0.2117$)
SSI	0.37102 ($P = 0.0147$)	-	0.23623 ($P = 0.1297$)	0.32725 ($P = 0.0362$)	-	0.29632 ($P = 0.0701$)
SAP	0.36011 ($P = 0.0225$)	0.23623 ($P = 0.1297$)	-	0.20959 ($P = 0.2117$)	0.29632 ($P = 0.0701$)	-

toring for suspected GERD using unspecific symptoms such as irritability and cough. To the best of our knowledge this is the first study in children to compare the correlation and concordance of the diagnostic classification between SAA parameters. Taken together SI, SSI and SAP show important disagreements in the diagnostic classification of normal and abnormal symptom-GER association. Within the different SAA parameters a weak correlation could be seen at most. This renders the interpretation of the SAA results and the diagnosis of GERD based on SAA parameters difficult as the detection of a pathologic symptom association depends on the SAA parameter chosen. Additionally, the comparison between different studies should be based on the same SAA parameters because our study shows that SI, SSI and SAP are not interchangeable.

Our study showed a higher frequency of non-acid GER (77%) compared to acid GER. This is comparable to the incidence of non-acid GER in infants found in the literature^[17]. The high proportion of non-acid GER in our study could also be explained by the fact that some of our patients were examined under treatment. To leave the patients under treatment while presenting GER-like symptoms reflects a clinical situation common in pediatric gastroenterology, as pediatric gastroenterologists are currently increasingly asked to evaluate a patient on proton pump inhibitor treatment after an unsuccessful medical trial. Condino *et al*^[5] found no relation between category of GER (acid or non-acid) and the association between GER and the symptoms irritability and cough. In that

study, 49.8% of fussiness and pain episodes (comparable to irritability) were related to GER, whereas in our study only 39% of the irritability symptoms were related to GER. In addition, it was reported that 33.5% of cough episodes were related to GER, whereas our study shows that 47% of cough episodes were related to GER.

While our findings are interesting, obviously the limitations of our study must be pointed out. As with many other studies investigating the role of MII in children, the sample size is rather small^[18]. Evaluation of the diagnostic classification did not show significant concordance. This is probably due to true discordance, but could also be due to a too weak study power. Furthermore, it must be noted that this study predominantly consists of male infants which reduces the possibility of generalizing the findings to female infants.

The question arises as to which of the three SAA parameters is the best for the diagnosis of GERD. To date the only study to evaluate the diagnostic accuracy of SI, SSI and SAP is a work by Taghavi *et al*^[19] on an adult study group. That study validated the SAA parameters obtained on 24 h pH-monitoring against a PPI treatment-trial dividing the study group into responders and non-responders. Patients were given a high dose of omeprazole treatment and asked to complete a symptom score before and after the treatment. Those who showed an effect were considered to have GERD. SSI, with an adapted cut-off value of 1.3%, showed the highest positive and negative predictive values, followed by SAP. SI had the poorest performance

with absence of a meaningful cut-off value making it almost useless. Despite the routine clinical use of SAA parameters in pediatrics there is currently no validation study for combined pH/MII monitoring. The problem is the lack of an objective gold-standard test for the detection of GERD, independent from combined pH/MII monitoring. In an analogy to the work of Taghavi *et al*^[19], we would need to perform a reference test in infants, with symptom scoring before and after treatment (e.g. proton pump inhibitors, prokinetics, surface agent, *etc.*) including combined pH/MII monitoring. This is ethically and methodologically challenging in infants.

In general use of SAA is hampered by numerous question marks concerning its accuracy. Firstly, it depends on a technique that correctly detects the GER events. It is likely that the introduction of combined pH/MII-monitoring adding the detection of non-acid GER events, compared to single pH-monitoring, makes SAA more accurate. A study of Rosen *et al*^[6] showed that significantly more children had a positive SI using combined pH/MII-monitoring, than using pH-monitoring alone. A possible shortcoming of the 24 h-monitoring technique is the fact that the number of acid and non-acid GER events in MII varied significantly on 2 consecutive days in an adult study^[20]. Additionally, investigating 48 h ambulatory pH-monitoring doubled the SI and SAP in adults with atypical GER symptoms compared to 24 h monitoring^[21]. Furthermore, automatic MII analysis considers only a drop of impedance of 50% or more as a GER event; however, it is very likely that a drop of 49% could also be attributed to a GER event^[4]. To date there are very few studies which evaluate the efficacy of automated analysis. A study by Roman *et al*^[22] in adults however showed good agreement between visual analysis and the automated analysis used in our study.

Secondly, results of SAA may have some methodological weaknesses. It depends on the active participation of the observers, in our case nurse and parents^[4], thus being impacted by the compliance and the variable work intensity on the ward. It has been shown that adults record only 39% of the cough episodes detected by simultaneous manometry^[23]. The arbitrary choice of the time window influences the symptom association parameters. The 5 min time window used within this automatic analysis tool and in other studies may not be optimal for the evaluation of symptoms such as irritability and cough. In this context one has to keep in mind, that SAA detects timely association, which does not necessarily mean causal relation. Unspecific symptoms in infants such as irritability and cough can be evoked by a large number of factors. The temporal association of GER and an unspecific symptom can therefore be a coincidence. SI and SSI have cut-off values that were arbitrarily chosen. In addition, they do not take into account the total number of GER episodes and total number of symptoms, respectively. Therefore, the SI can be positive simply because of a high number of GER episodes, whereas the SSI can be falsely positive because of a high number of symptoms^[18].

By showing poor inter-parameter association and important disagreements in diagnostic classification with the 3 established SAA parameters SI, SSI and SAP using combined pH/MII monitoring technique, we showed a common problem encountered with SAA, which is the difficulty of choosing the appropriate parameter to use. Our study cannot give an answer to this problem. Because of unanswered technological, methodological and validation questions and the limited concordance between the SAA parameters, we believe that at the moment, SAA based on combined pH/MII monitoring is a poorly reliable tool for the diagnosis of GERD. Diagnosis of GERD in infants with GERD-like symptoms therefore remains based on several elements such as the absence of more probable reasons for GERD-like symptoms, the positive response to treatment or the detection of GERD complications. However, combined pH/MII-monitoring can argue against GER as the origin of GERD-like symptoms, when showing absent or very low frequencies of GER episodes. Studies in infants are needed in order to obtain reference values and to adjust SI, SSI and SAP cut-off values for GERD, validated for the infant population.

COMMENTS

Background

Gastroesophageal reflux (GER), defined as passage of gastric contents into the esophagus is a normal process that occurs in healthy infants, children and adults. When GER causes troublesome symptoms and/or complications it is referred to as gastroesophageal reflux disease (GERD). During infancy GER is common and can manifest with specific symptoms as vomiting and non-specific symptoms as irritability and cough. Association of non-specific symptoms with GER is a main problem in the diagnosis of GERD.

Research frontiers

Combined pH/multiple intraluminal impedance (MII) detects GER episodes in the individual esophagus. The better the timely association of GER episodes and symptom episodes the more probable it is that GER is the origin of symptoms. Timely association of GER episodes and symptom episodes are expressed by symptom-reflux association analysis (SAA) parameters. Abnormal results of SAA parameters point towards GERD. Three SAA parameters are commonly used, symptom index (SI), symptom sensitivity index (SSI) and symptom association probability (SAP) but they were never validated for the diagnosis of GERD in the infant population. In this study the authors analyzed the agreement between SI, SSI and SAP.

Innovations and breakthroughs

This is the first study in infants to show an important disagreement between the 3 commonly used SAA parameters SI, SSI and SAP, which puts the accuracy of SAA into question. The study shows that the results of SI, SSI and SAP for the diagnosis of GERD often differ. In consequence, the diagnosis of GERD in infants cannot be based on a single SAA parameter as it remains unknown which SAA parameter is the most accurate for the diagnosis of GERD.

Applications

The limited agreement of these parameters must be taken into consideration when interpreting the results of SAA. The diagnosis of GERD should be based on a combination of pH/MII-monitoring, SAA results as well as on other factors such as clinical judgment, gastroscopy and follow-up under medical therapy. Validation studies to enhance the accuracy of SAA parameters and to answer the question which SAA parameter is the most accurate are needed.

Terminology

MII in combination with pH-measurement, a technique based on the fact that the passage of gastric content into the esophagus changes the impedance (electrical resistance) between esophageal segments, is more and more replacing the classic single pH-measurement as a diagnostic tool for GERD. A catheter with multiple impedance recording segments and one distal pH-electrode

connected to an exteriorly portable recording device is placed transnasally into the patient's esophagus in order to detect acid and nonacid GER events.

Peer review

This is an important topic and it has been little addressed in children.

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