

Impedance pH Monitoring: Intra-observer and Inter-observer Agreement and Usefulness of a Rapid Analysis of Symptom Reflux Association

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Background/Aims

Symptom reflux association analysis is especially helpful for evaluation and management of proton pump inhibitor (PPI) refractory patients. An accurate calculation requires manual editing of 24-hour multichannel intraluminal impedance-pH (MII-pH) tracings after automatic analysis. Intra- and inter-observer agreement as well as reliability of rapid editing confined to the time around symptomatic episodes are unknown. Aim of this study was to explore these topics in a prospective multicenter study.

Methods

Forty consecutive patients who were off PPI therapy underwent MII-pH recordings. After automatic analysis, their tracings were anonymized and randomized. Three experienced observers, each one trained in a different European center, independently performed manual editing of 24-hour tracings on 2 separate occasions. Values of symptom index and symptom association probability for acid and non acid reflux were transformed into binary response (i.e., positive or negative).

Results

Intra-observer agreement on symptom reflux association was 92.5% to 100.0% for acid and 85.0% to 97.5% for non-acid reflux. Inter-observer agreement was 100.0% for acid and 82.5% to 95.0% for non-acid reflux. Values for symptom index and symptom association probability were similar. Concordance between 24-hour and rapid (2 minutes-window before each symptomatic episode) editings for symptom reflux association occurred in 39 to 40 patients (acid) and in 37 to 40 (non-acid), depending on the observer.

Conclusions

Intra- and inter-observer agreement in classifying patients with or without symptom reflux association at manual editing of 24-hour tracings was high, especially for acid reflux. Classifying patients according to a rapid editing showed excellent concordance with the 24-hour one and can be adopted in clinical practice.

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Key Words

Esophageal pH monitoring; Inter-observer variability; Intra-observer variability

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Introduction

Esophageal 24-hour multichannel intraluminal impedance-pH monitoring (MII-pH) is currently considered the gold standard for evaluation of gastro-esophageal reflux disease (GERD). Its advantage over traditional pH-monitoring is the ability to detect weakly acidic reflux episodes in addition to acid reflux and also to differentiate among liquid, gaseous and mixed liquid/gaseous refluxes.¹ Observations with this technique have shown the clinical relevance of weakly acidic reflux especially in patients poorly responsive to proton pump inhibitors (PPI).²⁻⁴

Whereas pH-monitoring analysis is automatic and very quick, analysis of MII-pH tracings is much more time consuming because it needs manual revision of tracing after the automatic analysis, especially because events other than reflux are included among reflux episodes by the software. Automatic analysis particularly overestimates the number of non-acid reflux events resulting in a lower sensitivity and specificity of a positive symptom index (SI) compared to visual analysis.⁵ Moreover a low baseline impedance, which may be observed especially in presence of erosive esophagitis or Barrett's esophagus^{6,7} makes the analysis more difficult and the mistakes easier to occur.

Information resulting from MII-pH is important especially in patients refractory to PPIs because it guides medical treatment and may suggest usefulness of anti-reflux surgery. Both a quantitative (i.e., number of reflux episodes) and a qualitative analysis (i.e., symptom reflux association) should be performed, the latter analysis having a higher relevance in PPI refractory patients who frequently have a normal number of reflux episodes.^{2,3} Studies on intra- and inter- observer agreement of manual analysis are scanty, small, referred to the paediatric population or to healthy adults,⁸⁻¹¹ and they have focused on number of reflux episodes only.

In clinical practice physicians often concentrate their editing in the time window around symptomatic episodes in order to save time, however there are so far no data on reliability of such a partial, quick analysis of MII-pH tracings.

Aims of this study were to evaluate: (1) agreement within and between 3 experienced observers trained in different European Centers for presence/absence of symptom reflux association according to currently used indexes and for detection of individual reflux episodes and (2) concordance between the traditional 24-hour manual analysis and a quicker one for presence/absence of symptom reflux association.

Materials and Methods

Patient Population

Between September 2011 and January 2012 forty consecutive patients off PPI therapy with typical (i.e., heartburn and regurgitation) and/or atypical (i.e., chest pain) esophageal or extra-esophageal (i.e., cough) symptoms possibly related to GERD, who have undergone 24-hour MII-pH in 2 Centers in Northern Italy (Milan and Verona) and have reported symptomatic episodes during the test, were prospectively enrolled. Each center has provided 20 MII-pH tracings. The study protocol has been approved by the Ethics Committees of both hospitals.

Impedance-pH Equipment

Esophageal MII-pH monitoring was performed using a MII-pH catheter (Z61A; Medical Measurement Systems, Enschede, The Netherlands) containing one distal antimony pH electrode and eight impedance electrode rings at 2, 4, 6, 8, 10, 14, 16 and 18 cm from the tip of the catheter. Each pair of adjacent electrodes represents an impedance-measuring segment (2 cm in length) corresponding to one recording channel. The eight impedance and pH signals were recorded at 50 Hz on a 128 MB Compact Flash Card. Data were stored in a portable receiver with impedance amplifier (Medical Measurement Systems).

Study Protocol

After an overnight fast, patients attended the Upper Gastrointestinal (GI) Physiology Unit of both Centers. Patient's medical history was collected and informed consent was signed. The lower esophageal sphincter (LES) was located by esophageal manometry and the MII-pH catheter was passed trans-nasally under topical anaesthesia and positioned with the pH electrode 5 cm above the upper border of the LES. During a MII-pH monitoring, patients were asked to report timing of meals and periods spent in recumbent position on a daily diary card; when a symptom occurred patients were asked to push a button on the portable receiver and to report the exact time on the diary card. When many symptoms were reported, only the principal symptom was taken into account. During the recording period patients were allowed to have a free diet, except for known acidic food and beverages, and to continue their usual daily activities. Patients returned to the Upper GI Physiology Unit on the following morning for catheter removal.

All tracings were read twice by the three observers, each one trained in a different Center (London, Milan and Verona). The three observers were all experienced in the analysis of MII-pH tracings, having previously analyzed at least 200 tracings and performing at least 70 MII-pH/year. The second reading of each tracing was performed at least 12 weeks after the first one.

Data Analysis

Data stored on the Compact Flash Card were downloaded into a personal computer. Markers of meal periods and of timing in recumbent position were manually inserted. Data were analysed by using an automated reflux detection algorithm (Medical Measurement Systems) and meal periods were excluded from the analysis. Original tracings were anonymized and numbered from 01 to 20 (provided by Milan) and from 41 to 60 (provided by Verona) for inter-observer agreement analysis. These tracings were subsequently duplicated and numbered in a randomized order from 21 to 40 and from 61 to 80 for intra-observer agreement analysis. Each tracing was named adding a code identifying the Center in order to distinguish those reviewed by each observer (observer 1 from Milan, observer 2 from Verona and observer 3 from London). In order to identify tracings difficult to analyse, baseline impedance of each tracing was measured before manual analysis. Baseline esophageal impedance was assessed as a mean baseline at the two most distal impedance channels (situated at 3 and 5 cm above the LES), considering a 5-minutes window period during the night. Baseline impedance was considered low if $< 500 \Omega$.^{7,12} The traditional 24-hour manual analysis was performed as follows. Each observer went through every reflux episode and, when he/she did not agree with the automatic analysis, the reflux episode was erased; furthermore reflux episodes not recognized by the automatic analysis were added. In order to avoid a possible bias due to variability of a further analysis, the rapid analysis was obtained by checking for changes that each observer had made during his/her 24-hour analysis in the 2-minute window period preceding each symptom and copying them in a separate automated analysis file.

Definitions

Reflux episodes

Only liquid and mixed liquid-gas reflux episodes according to impedance changes were included in the analysis. These reflux episodes were classified by pH drop nadir in: (1) acid reflux: impedance-detected reflux event with a nadir pH less than 4, (2)

weakly acid reflux: impedance-detected reflux event with a nadir pH between 4 and 6, and (3) weakly alkaline reflux: impedance-detected reflux event with a nadir pH above 7.¹ As weakly alkaline refluxes are very infrequent, in the analysis they were merged with weakly acidic refluxes and considered as non-acid reflux. Total number of reflux episodes was considered pathological when $\geq 75/24$ hours.¹³

Symptom-reflux association

SI and symptom association probability (SAP) were automatically calculated by the software in each patient. Only the association between the principal symptom reported by the patient and acid and non-acid reflux was reported. SI and SAP were defined according to Wiener et al¹⁴ and Weusten et al,¹⁵ respectively. SI was considered positive when $\geq 50\%$ and SAP when $\geq 95\%$.

Statistical Methods

Intra-observer repeatability and inter-observer reproducibility of esophageal 24-hour pH-impedance analysis were expressed as percentage of agreement and as Cohen's kappa statistic. These measures were applied to agreement on positive/negative symptom-reflux association and on individual reflux episodes. A kappa equal to 0 meant that the agreement was no better than that expected by chance alone, and a kappa values equal to 1 indicated perfect agreement.

Table 1. Variables of the 40 Multichannel Intraluminal 24-hour Impedance-pH Tracings as Assessed by the 3 Observers

	Observer 1 (Milan)	Observer 2 (Verona)	Observer 3 (London)
AC reflux episodes (median [range])	25 (1-90)	22 (0-83)	25 (1-91)
NA reflux episodes (median [range])	19 (2-89)	8 (1-76)	21 (2-99)
Total reflux episodes (median [range])	44 (5-99)	28 (1-89)	49 (4-106)
Positive SI for AC (n [%])	5 (12.5)	5 (12.5)	5 (12.5)
Positive SI for NA (n [%])	2 (5.0)	0 (0.0)	1 (2.5)
Positive SAP for AC (n [%])	6 (15.0)	5 (12.5)	6 (15.0)
Positive SAP for NA (n [%])	8 (20.0)	2 (5.0)	5 (12.5)

AC, acid; NA, non acid; SI, symptom index; SAP, symptom association probability.

Table 2. Kappa Values With Standard Error Between the First and the Second Analysis, With Regards to Symptom Index and Symptom Association Probability Divided Into Acid/Non acid

	SI		SAP	
	Acid	Non acid	Acid	Non acid
Observer 1	0.77 (0.15)	0.65 (0.31)	0.80 (0.13)	0.48 (0.18)
Observer 2	0.77 (0.15)	- ^a	0.72 (0.15)	0.79 (0.20)
Observer 3	1.00 (0.00)	- ^a	1.00 (0.00)	0.54 (0.20)

^aKappa coefficient could not be calculated because all results were negative in the second analysis.

SI, symptom index; SAP, symptom association probability. Data are presented as kappa coefficient (standard error).

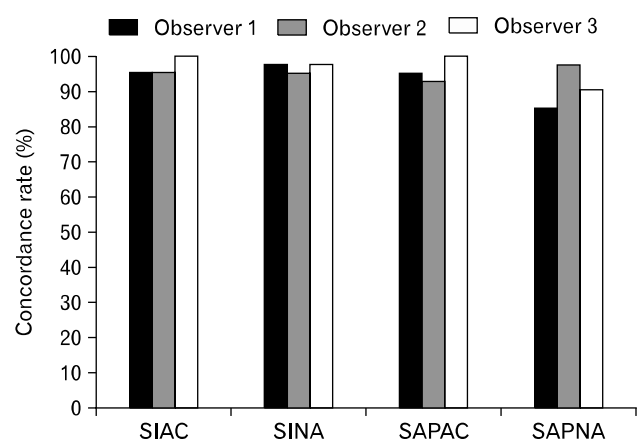


Figure 1. Percentage of concordance between the first and the second analysis, with regards to symptom index (SI) and symptom association probability (SAP) divided into acid (AC) and non-acid (NA) reflux.

Results

Patients Characteristics

Twenty-three of the 40 enrolled patients were women and the median age was 55 years (range, 27 to 88 years). All patients completed the study and the recording period was more than 23 hours in all of them. Seventeen (42.5%), 7 (17.5%) and 16 patients (40%) experienced typical symptoms, chest pain and cough, respectively. All patients had a previous upper GI endoscopy showing grade A erosive esophagitis in 5/40 patients (12.5%). No Barrett’s esophagus was detected. No patients had a low esophageal impedance baseline with the median value being 2487 Ω (range, 662-5548 Ω). Table 1 shows variables of the 40 MII-pH tracings as assessed by the 3 observers. The total num-

Table 3. Kappa Values With Standard Error Between Observers, With Regards to Symptom Index and Symptom Association Probability Divided Into Acid/Non acid

	SI		SAP	
	Acid	Non acid	Acid	Non acid
Observer 1 vs. Observer 2	1.00 (0.00)	- ^a	1.00 (0.00)	0.35 (0.19)
Observer 1 vs. Observer 3	1.00 (0.00)	- ^a	1.00 (0.00)	0.36 (0.19)
Observer 2 vs. Observer 3	1.00 (0.00)	- ^a	1.00 (0.00)	0.23 (0.23)

^aKappa coefficient could not be calculated because all results were negative for observer 1 and 2.

SI, symptom index; SAP, symptom association probability. Data are presented as kappa coefficient (standard error).

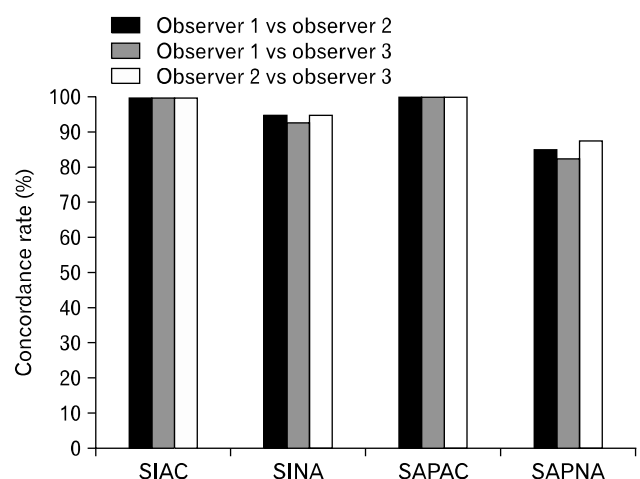


Figure 2. Percentage of concordance between observers, with regards to symptom index (SI) and symptom association probability (SAP) divided into acid (AC) and non-acid (NA) reflux.

ber of reflux episodes was more than 75 in 5/40 (12.5%), 2/40 (5%) and 5/40 (12.5%) tracings for observer 1, 2 and 3, respectively.

Agreement for Symptom/Reflux Association

Intra-observer (see Table 2 and Fig. 1)

Agreement between the first and the second analysis was generally high for all 3 observers and slightly better for acid compared to non-acid refluxes.

Inter-observer (see Table 3 and Fig. 2).

Agreement between the 3 observers was generally good, although it was higher for acid refluxes compared to non-acid ones.

Agreement for Detection of Individual Reflux Episodes

Intra-observer

Median intra-observer agreement between first and second analysis was 98.2% (range, 92.4-99.6%) for acid episodes with a median kappa coefficient of 0.68 whereas it was 92.3% (range, 82.1-92.4%) for non-acid episodes with a median kappa coefficient of 0.40. Intra-observer agreement for judging a study normal or pathological on the basis of the number of reflux episodes was almost perfect for all the observers, as the number of studies with a pathological number of reflux episodes remained the same for observer 2 and increased from 5 to 6/40 for observer 1 and 3 in the second analysis.

Inter-observer

Median inter-observer agreement was 86.8% (range, 86.3-97.6%) for acid episodes with a median kappa coefficient of 0.22. Median agreement was lower for non-acid episodes, 55.7% (range, 48.9-81.5%) with a median kappa of 0.19.

Symptom Reflux Association: Concordance Between 24-hour and a Rapid Analysis

Rapid editing showed to be highly predictive of the traditional 24-hour one for all 3 observers with regards to the four symptom reflux association variables (Table 4). In particular rapid and traditional 24-hour editing showed concordance in 39 (97.5%) to 40

Table 4. Percentage of Concordance With Confidence Interval Between Short and Traditional Analysis

	SI		SAP	
	Acid	Non-acid	Acid	Non-acid
Observer 1	100.0 (91-100)	100.0 (91-100)	100.0 (91-100)	97.5 (85-100)
Observer 2	97.5 (85-100)	95.0 (82-99)	97.5 (85-100)	92.5 (78-98)
Observer 3	97.5 (85-100)	100.0 (91-100)	100.0 (91-100)	100.0 (91-100)

SI, symptom index; SAP, symptom association probability. Data are presented as percentage of concordance (confidence interval).

(100.0%) patients for acid reflux and in 37 (92.5%) to 40 (100.0%) for non-acid reflux, depending on the observer.

Discussion

Results of our study showed that intra- and inter-observer agreement for presence or absence of a symptom-reflux association was high, though slightly lower for non acid (82.0-97.5%) than for acid reflux (92.0-100.0%). Furthermore, and more interestingly from a practical point of view, a rapid analysis of symptom reflux association confined to the time around symptomatic episodes was highly predictive of the analysis performed over 24 hours.

Evaluation of symptom/reflux association is the most useful variable in the analysis of MII-pH monitoring performed in patients referred to specialized Centers, who are frequently PPI resistant and often with normal reflux exposure.^{2,3,16} When symptom reflux association is negative both for acid and non-acid reflux in a patient with normal reflux the diagnosis of GERD is ruled out and anti-reflux surgery is no longer indicated as a therapeutic option. Automatic analysis by computer software has a rather low reliability for classifying patients as having positive or negative symptom reflux association because it overestimates reflux episodes^{5,8,10} and especially weakly acid reflux,⁵ when compared to manual analysis. This is why tracings are manually edited by a physician after automatic analysis, a routine which opens to possible inaccuracies due to intra and inter-observer variability, which have never been evaluated.

Our study is the first one which has focused on this topic and has shown good agreement both within each observer and among observers. Results of kappa statistics were less satisfactory especially regarding non-acid reflux because the vast majority of patients had a negative symptom reflux association and it is known that the imbalance between the 2 options of a binary response weakens this statistical analysis. Furthermore, kappa was not calculated for non acid reflux on 5 occasions, because all patients had a negative symptom reflux association. Our series is similar to previous ones, where esophageal symptoms were frequently found to be functional.¹⁷

Our study investigated also intra- and inter-observer agreements on number of acid and non-acid reflux episodes. Previous studies have addressed this topic in the paediatric^{8,9} and in the adult healthy¹¹ and GERD population,¹⁰ although the 2 latter studies looked at inter-observer agreement only. Furthermore in the paper by Ravi et al¹⁰ analysis was limited to classifying trac-

ings with either normal or pathological number of reflux episodes. In the report by Loots et al⁸ 10 tracings were analysed and inter-observer agreement was calculated among 10 assessors whereas intra-observer agreement was measured among 3 of them. In the report by Pilic et al⁹ 24 tracings were analysed for inter-observer agreement and 6 for intra-observer agreement between 2 investigators. In the study by Zerbib et al¹¹ 20 tracings off PPIs and 18 on PPIs obtained from 20 healthy subjects were evaluated for agreement between 2 observers. It is not easy to compare previous reports with ours because those studies considered all reflux episodes together, i.e., without separating acid and non-acid reflux, and data were presented in different formats. Regarding inter-observer agreement, the 2 observers in the study by Pilic et al⁹ had an agreement which varied widely among the 24 tracings, from 0 to 98% with a median of 73%, whereas the 2 observers in the study by Zerbib et al¹¹ had an overall agreement of 84% off PPIs and 73% on PPIs. Our results, obtained analyzing 40 tracings, showed lower inter-observer agreement on number of non-acid compared to acid reflux episodes (48.9-81.5% vs. 86.3-97.6%). This result was presumably mainly related to observer 2 scoring a lower number of non-acid refluxes, a fact which was likely to have also contributed to a lower inter-observer agreement on symptom reflux association for non-acid in comparison with acid reflux. Episodes of non-acid reflux are thus more challenging to be agreed upon both between software and an experienced assessor⁵ and among experienced assessors. Reasons for this have not been explored in detail, however absence of a clear drop in pH in situations where impedance readings are more difficult to be interpreted, i.e., unclear flow direction, flow after a swallow, possible reflux during low baseline impedance and patterns containing gas, presumably are important variables.¹⁸ These observations should stimulate on one hand the manufacturers to improve the software used for automatic analysis and on the other the training Centers to more carefully train physicians approaching this clinical field. Consensus meetings among experts with the aim to propose patterns to be detected as gastroesophageal reflux in MII-pH tracing are welcome in order to improve both automatic analysis and inter-observer agreement.¹⁸ A lower agreement for number of reflux episodes has been suggested in technically challenging tracings in children and infants.⁸ We have measured baseline impedance in order to classify tracings of technical difficulty, although others have suggested additional variables,¹⁸ and found that none was challenging because baseline impedance was $> 500 \Omega$ in all tracings. Our finding is in agreement with previous data,^{6,19} the vast majority of our patients

being endoscopy negative and with low acid exposure.

A drawback of manual editing after automatic analysis is that reviewing the whole tracing is time consuming and a quicker analysis confined to the time around symptomatic episodes has been advocated in clinical practice. This is why we think that the clinically more relevant information coming from our paper is that presence/absence of symptom reflux association determined after a rapid analysis of MII-pH recordings, i.e., centered in a 2-minute time window before symptomatic episodes, was highly predictive of results after the complete 24-hour analysis. This was true both for acid and non-acid reflux. Our observation thus strongly suggests reliability of a quick manual editing, which would save physician's time and Health Care System resources.

In conclusion, results of our prospective multicenter study have shown good intra-observer and inter-observer agreement for positive/negative symptom reflux association, when MII-pH tracings are manually edited after automatic analysis. This related both to acid and non-acid reflux, although inter-observer agreement was lower for non-acid reflux. Furthermore they have produced evidence that a rapid manual editing of the automatic analysis confined to a short time window before each symptomatic episode is highly reliable and can be adopted in routine clinical practice.

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