Application of Lyon Consensus criteria for GERD diagnosis - Evaluation of conventional and new impedance-pH parameters

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Running Title – Application of Lyon Consensus

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ABSTRACT

OBJECTIVE To validate Lyon Consensus criteria for diagnosing gastroesophageal reflux disease (GERD) by reflux monitoring.

METHODS Manual review of impedance-pH tracings from patients with proton pump inhibitor (PPI)-dependent heartburn, evaluated off PPI. Acid exposure time (AET) thresholds defined by the Lyon Consensus and impedance parameters were investigated, namely total refluxes (TRs), post-reflux swallow-induced peristaltic wave (PSPW) index and mean nocturnal baseline impedance (MNBI).

RESULTS The study included 488 patients, 178 (36%) with normal (<4%) AET, 89 (18%) with inconclusive (4-6%) AET, and 221 (45%) with abnormal (>6%) AET, alongside with 70 healthy controls. At receiver operating characteristic (ROC) analysis, the area under curve was 0.89, 0.95 and 0.89 for TRs, PSPW index and MNBI, respectively, and threshold values were 40, 50% and 2000Ω; the 4% physiologic AET threshold defined by the Lyon Consensus showed 100% specificity but 63% sensitivity. The thresholds defined for impedance parameters were validated against AET by means of ordered logistic regression, being in concordance with the 4% AET threshold (odds ratio 2.5 for TRs, 18.9 for PSPW index and 5.7 for MNBI). TRs positivity and concordant PSPW index/MNBI positivity were found in 80-90% of patients in the abnormal AET group, in 73-74% of cases in the inconclusive AET group, and in 28-40% of cases in the group with normal AET.

CONCLUSIONS Our results show the validity of the Lyon Consensus approach to GERD diagnosis. Adding evaluation of impedance parameters, namely TRs, PSPW index and MNBI to AET appraisal substantially improves the diagnostic yield of reflux monitoring.

KEY WORDS: GERD; Impedance-pH monitoring; PSPW index; Mean nocturnal baseline impedance.

STUDY HIGHLIGHTS

WHAT IS CURRENT KNOWLEDGE

- Reflux monitoring has been regarded as the test of choice to document GERD in patients with endoscopy-negative heartburn.
- A hierarchical approach to reflux monitoring has been proposed based on acid exposure time (AET) and supportive impedance parameters to confirm or exclude GERD.

WHAT IS NEW HERE

- Impedance parameters, namely total refluxes (TRs), post-reflux swallow-induced peristaltic wave (PSPW) index and mean nocturnal baseline impedance (MNBI) showed high efficiency in distinguishing patients with PPI-dependent heartburn from healthy controls.
- In the vast majority of patients with inconsistent AET values, GERD diagnosis was confirmed by impedance parameters.
- In approximately one third of patients with normal AET values, GERD diagnosis was confirmed by impedance parameters.
- Impedance parameters substantially increase the diagnostic yield of reflux monitoring, showing the high clinical value of impedance-pH monitoring for GERD diagnosis.

Introduction

Gastroesophageal reflux disease (GERD) develops when the reflux of gastric contents into the esophagus leads to troublesome symptoms and/or complications [1,2]. Heartburn is the most sensitive and specific GERD symptom with an estimated prevalence of 15-20% in the general population. Proton pump inhibitor (PPI) therapy represents the mainstay of medical treatment, relieving heartburn in most cases, so that in the absence of alarm symptoms heartburn relief by a 4-week PPI trial is regarded as sufficient to confirm GERD diagnosis in clinical practice [1,2].

Heartburn quickly recurs after PPI withdrawal, however, and many patients become PPI dependent. Side effects by PPI therapy have been claimed in recent years, and strategies for discontinuing long-term PPI therapy have been suggested [3]. Thus, many patients are referred to tertiary care centers for objective documentation of GERD in order to justify long-term PPI assumption, and several patients ask for surgical GERD management to get rid of PPI dependence despite confirmed evidence of the high safety of PPIs [4,5].

Objective GERD diagnosis is challenging since a definite gold standard has not yet been recognized. In the PPI era, endoscopy reveals erosive reflux esophagitis in a minority of patients referred for heartburn, then direct reflux monitoring is required in the majority of cases [6] to document abnormal reflux burden. Acid exposure time (AET) has long been regarded as the most useful parameter for this purpose, despite detection of normal values in up to 20% of patients with reflux esophagitis [7,8]. Currently, reflux monitoring can be performed with pH- or impedance-pH monitoring, the latter allowing detection of all reflux episodes independent of their acidity [9]. In recent years, new impedance parameters have been introduced, namely post-reflux swallow-induced peristaltic wave (PSPW) index [10], representing esophageal chemical clearance, and mean nocturnal baseline impedance (MNBI) [11], representing esophageal mucosal integrity, both reportedly increasing the diagnostic yield of impedance-pH monitoring [12]. Following expert meetings, reference threshold AET values have been agreed upon [13] and recommended by the Lyon Consensus [14]: AET >6% and <4% were regarded as definitely abnormal and normal,

respectively, whilst values between 4% and 6% were considered as inconclusive and necessitating supportive evidence by adjunctive parameters, including number of total refluxes (TRs), symptom association probability (SAP) and symptom index (SI) as well as the new metrics PSPW index and MNBI.

In the present study, we report the results of the application of the Lyon Consensus criteria in a large cohort of patients prospectively evaluated at referral centers for PPI-dependent heartburn. Our aim was to define the clinical value of conventional and new impedance parameters as compared to the AET threshold values proposed by the Lyon Consensus.

Methods

Data collected at Italian referral centers between January 2016 and January 2021 were reviewed. The study was designed and performed in accordance with the Declaration of Helsinki. Since patients were investigated for clinical reasons and were not exposed to any additional intervention for research purposes, according with Italian law formal medical ethical assessment was not required. A signed informed consent was obtained before any clinical investigation. Heartburn was scored using a validated four-grade Likert-type scale, administered by a senior investigator [15]. Briefly, heartburn was scored 0 when absent, 1 when mild/occasional, 2 when moderate/frequent, and 3 when severe/constant, and was considered troublesome for score 2 or 3. Previous esophagogastric surgery, psychiatric disorders, Sjogren syndrome, scleroderma, as well as Barrett's esophagus and reflux esophagitis (grade B-C-D Los Angeles score) at upper GI endoscopy constituted exclusion criteria. Patients were referred for possible antireflux surgery or for confirmation of the appropriateness of long-term PPI treatment. They were considered to have PPI-dependent heartburn if reporting a history of troublesome heartburn (score 2-3) suppressed (score 0-1) by 4-week standard-dosage PPI therapy, early recurring after PPI wash-out and again early suppressed by 4-week standard-dosage PPI. Impedance-pH monitoring was carried out after 2-week

PPI withdrawal and was always preceded by conventional or high-resolution esophageal manometry to exclude major motor disorders [16].

Impedance-pH probes allowed detection of intraluminal impedance at 3, 5, 7, 9, 15, and 17 cm and of pH at 5 cm above the upper border of the manometrically defined lower esophageal sphincter. Tracings were manually reviewed by senior investigators, aided by the BioView® software (Diversatek/Sandhill Scientific, Colorado, USA) and following rigorous rules to identify total refluxes (TRs) and PSPWs [17]. According to the Lyon Consensus, AET was regarded as definitely abnormal for values >6%, definitely normal for values <4%, and inconsistent for values between 4% and 6%; positive heartburn–reflux association was defined for combined positivity of symptom-association probability (SAP) and symptom index (SI), i.e. >95% and >50%, respectively [13,14]. A PSPW was defined as an antegrade 50% drop in impedance originating in the proximal esophagus within 30 s after the end of a reflux event and reaching the distal lumen [17]; dividing the number of PSPWs by the number of TRs, the PSPW index was obtained [10]. MNBI was assessed in the nighttime recumbent period from the most distal impedance channel; three 10-min time intervals (around 1.00 am, 2.00 am, and 3.00 am) were selected avoiding swallows, refluxes and pH drops, and the mean was calculated [11]. Impedance-pH parameters of patients with PPI-dependent heartburn were categorized according to AET threshold values as proposed by the Lyon Consensus and compared with those of 70 healthy controls.

Statistics

Continuous and categorical variables were compared with ANOVA and chi-square test, respectively. Receiver operating characteristic (ROC) analysis with calculation of the area under the curve (AUC) was used to assess the diagnostic yield of conventional and novel impedance-pH parameters comparing PPI-dependent patients with healthy controls; thresholds of TRs, PSPW index, and MNBI were established favoring specificity over sensitivity. Ordered logistic regression analysis was then applied to validate the thresholds of TRs, PSPW index, and MNBI against the

diagnostic categories as defined by the AET thresholds: for each impedance-pH variable, odds ratio (OR) was computed alongside with 95% confidence interval (CI), representing the probability of upgrading from a lower to a higher diagnostic category. STATA statistical software, release 16 (STATA, College Station, TX) was used. Significance was set at $P < .05$, adjusted with Bonferroni correction for multiple comparisons.

Results

The main baseline characteristics of the 488 patients with PPI-dependent heartburn included in the study are reported in Table 1 alongside with those of 70 healthy controls. Heartburn was not recorded during impedance-pH testing by 95 of 488 (19%) cases; SAP and SI were both positive in 214 (44%) cases. At ROC analysis, the AUC of AET was 0.92 (95% CI 0.90-0.95), quite similar to those of TRs, PSPW index and MNBI (Figure 1). The threshold values resulting from maximizing the sum of sensitivity and specificity and favoring the latter were 40 for TRs, 50% for PSPW index and 2000Ω for MNBI.

The AET thresholds values proposed by the Lyon Consensus [14] were used to categorize the 488 PPI-dependent heartburn cases into normal AET (<4%) (178 cases, 36%), inconclusive AET (4-6%) (89 cases,18%) and abnormal AET (>6%) (221 cases, 45%) group: the mean values of TRs, PSPW index and MNBI in the three groups are reported in Table 2. AET was <4% in all healthy controls; at ROC analysis, the 4% AET physiologic threshold proposed by the Lyon Consensus had a 100% specificity and a 63% sensitivity.

Results of ordered logistic regression are reported in Table 3. The impedance parameters, namely TRs, PSPW index and MNBI were validated against AET: higher values of such parameters were significantly associated to higher values of AET, in concordance with the thresholds defined by the Lyon consensus, the highest OR being displayed by PSPW index.

Table 4 shows positivity of impedance parameters in the 488 PPI-dependent heartburn cases as subdivided according to normal, inconclusive and abnormal AET. Concordant positivity of SAP and SI was quite similar comparing the three groups. Abnormal values of TRs, PSPW index, and MNBI were significantly more frequent in the inconclusive and abnormal AET group as compared with the normal AET group. Concordant positivity of PSPW index and MNBI was significantly higher in the abnormal and inconsistent than in the normal AET group ($P < .05$) (Figure 2).

Discussion

In this large multicenter cohort of patients with PPI-dependent heartburn, we defined threshold values of TRs, PSPW index and MNBI through ROC analysis. All three metrics efficiently separated patients with normal AET from those with inconclusive and abnormal AET as defined by the Lyon Consensus [14]: indeed, significant difference in mean values among the three groups were detected, and all the three metrics were validated against AET.

In the present series, concordant SAP/SI positivity was detected in less than half of our patients and did not differ among the three AET groups, indicating the lack of relationship with acid reflux burden. SAP and SI are considered complementary, and concordant positivity is regarded to show the best link between symptoms and reflux [13,14]. However, SAP and SI are overly dependent on patient's recording accuracy, and symptoms are not recorded during reflux monitoring in many cases: then, assessment of more objective parameters is warranted for a firm diagnosis of GERD.

The diagnostic value of TRs has not yet been thoroughly investigated in patients complaining of heartburn. On PPI, TRs positivity was detected in more than half of patients with PPI-refractory heartburn who underwent successful antireflux surgery [15]. Recently, it has been suggested that TRs may represent a predictor of GERD treatment outcome [18]. In the present study, TRs positivity was detected in much more cases in the inconsistent and abnormal AET than

in the normal AET group, showing that this parameter can be useful in the diagnostic work-up for patients with the typical GERD syndrome.

The high diagnostic yield of combined assessment of PSPW index and MNBI has been shown by several studies [11,12,15,19-26]. PSPW index represents esophageal chemical clearance, a major defense mechanism against reflux elicited by the esophago-salivary reflex [27], in turn directly related to the potential harmfulness of refluxate [28], while MNBI represents mucosal integrity, lower values of both parameters reflecting increasing GERD severity [12]. PSPW index does not improve significantly after effective antireflux surgery, in turn confirmed by subtotal abolition of TRs, whereas normalization of mucosal integrity as measured with MNBI occurs in nearly all cases [15]: these findings suggest that impairment of chemical clearance should be considered as clinically relevant when associated with detectable mucosal damage documented by low MNBI values [20,22,23]. The diagnostic efficiency of PSPW index and MNBI was confirmed in the present series, with concordant positivity detected in much more cases in the inconclusive and in the abnormal than in the normal AET group.

Nearly half of our patients had AET >6%, the threshold defined by the Lyon Consensus as conclusive evidence of pathologic reflux [14]; TRs and concordant PSPW index/MNBI positivity was found in 80% and 90% of these cases, respectively, confirming the validity of the >6% AET threshold, which can then stand alone for confirming GERD diagnosis in patients with endoscopy-negative heartburn. The inconsistent AET group comprised less than one fifth of our patients: GERD diagnosis was confirmed by TRs positivity and concordant PSPW index/MNBI positivity in three fourths of cases, showing the high usefulness of these impedance metrics in such cases.

More than one third of our patients had AET <4%, to be considered as evidence against pathologic reflux according to the Lyon Consensus [14]. However, in our series of 488 PPI-dependent heartburn cases and 70 healthy controls, the AET 4% threshold showed a 100% specificity but a 63% sensitivity. The latter finding can be explained with the well-recognized limitations in diagnostic sensitivity of AET [7,8], in part due to day-to-day variability as shown by

prolonged wireless pH monitoring [29]. We found TRs positivity and concordant PSPW index/MNBI positivity in approximately one third of patients with AET <4% and PPI-dependent heartburn, and we believe that in such cases GERD diagnosis should not be dismissed and long-term PPI treatment can be considered appropriate.

Reflux monitoring has been recommended off PPI when GERD is unproven, and the choice between catheter-based/wireless pH-monitoring and pH-impedance monitoring has been suggested on the basis of cost and availability [14]. The Lyon Consensus proposed a hierarchical approach to GERD diagnosis based on defined AET thresholds, while SAP/SI positivity, abnormal number of TRs, and low values of PSPW index and MNBI were considered as supportive evidence for GERD diagnosis in case of inconclusive AET values [14]. Actually, among the parameters supporting inconclusive AET only SAP and SI for acid refluxes can be assessed with catheter-based/wireless pH-monitoring while TRs, PSPW index and MNBI can be assessed only with impedance-pH monitoring. Therefore, only impedance-pH monitoring provides a comprehensive evaluation of total reflux burden (TRs), of the reaction against reflux (PSPW index) and of the consequences of reflux (MNBI). Since our results show the high diagnostic yield of these parameters, it can be inferred that impedance-pH monitoring is the test of choice for reflux monitoring in order to diagnose GERD.

A few limitations of our study should be acknowledged. Threshold values for TRs, PSPW index and MNBI found in the present series are at minor variance with those previously suggested [12], a result probably due to the smaller size of that series and to the subsequent development of consensus criteria about definition of reflux episodes [17], in turn directly influencing calculation of PSPW index. Refinements of software automated analysis, possibly aided by artificial intelligence, are needed to simplify analysis and interpretation of impedance-pH monitoring. We focused on heartburn since it is the cardinal symptom of the typical GERD syndrome [1], often becoming dependent on long-term PPI treatment: it remains to be established the applicability of our findings in patients with non-cardiac chest pain and extraesophageal reflux symptoms.

In conclusion, our results show the overall validity of the hierarchical approach for diagnosis of GERD as proposed by the Lyon Consensus and based on AET threshold values [14]. The diagnostic yield of reflux monitoring is substantially improved by assessment of impedance parameters, namely TRs, PSPW index and MNBI, indicating that impedance-pH monitoring represents the most informative reflux-monitoring test for GERD diagnosis.

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Table 1. Baseline characteristics of 488 patients with PPI-dependent heartburn and of 70 healthy controls

	PPI-dependent heartburn	Healthy controls	P
Male gender (n) (%)	232 (48%)	45 (64%)	.013
Age (years) (mean) (SD)	50 (14)	40 (14)	< .0001
AET (%) (mean) (SD)	6.7 (5.9)	0.9 (0.9)	< .0001
TRs (n) (mean) (SD)	58 (38)	21 (14)	< .0001
PSPW index (%) (mean) (SD)	31 (18)	72 (17)	< .0001
MNBI (Ω) (mean) (SD)	1565 (837)	2990 (835)	< .0001
Concordant SAP/SI positivity (n) (%)	214 (44%)	/	/

PPI, proton pump inhibitor; AET, acid exposure time; TRs, total refluxes: PSPW, post-reflux swallow-induced peristaltic wave; MNBI, mean nocturnal baseline impedance; SAP, symptom association probability; SI, symptom index.

Table 2. Mean impedance metrics in 488 patients with PPI-dependent heartburn as categorized by the Lyon Consensus AET thresholds

	Normal AET (<4%) (n=178) (36%)	Inconclusive AET (4-6%) (n=89) (18%)	Abnormal AET (>6%) (n=221) (45%)
TRs (n) (mean) (SD)	42 (26)	66 (54)	69 (35)
P < .05 for normal AET group vs. inconclusive AET and abnormal AET group			
PSPW index (%) (mean) (SD)	45 (18)	28 (12)	22 (12)
P < .05 for all pairwise comparisons			
MNBI (Ω) (mean) (SD)	2103 (830)	1571 (704)	1127 (609)
P < .05 for all pairwise comparisons			

PPI, proton pump inhibitor; AET, acid exposure time; TRs, total refluxes; PSPW, post-reflux swallow-induced peristaltic wave; MNBI, mean nocturnal baseline impedance; *p* value adjusted with Bonferroni correction for multiple comparisons.

Table 3. Ordered logistic regression assessing threshold values of impedance metrics against the diagnostic categories defined by normal, inconsistent and abnormal AET

	OR	95% CI
TRs >40	2.5	1.6 - 4.0
PSPW index <50%	18.9	8.6 - 41.3
MNBI <2000 Ω	5.7	3.7 - 8.8

OR, odds ratio; CI, confidence interval; TRs, total refluxes; PSPW, post-reflux swallow-induced peristaltic wave; MNBI, mean nocturnal baseline impedance.

Table 4. Positivity of impedance parameters in 488 patients with PPI-dependent heartburn as categorized by the Lyon Consensus AET thresholds

	Normal AET (<4%)	Inconclusive AET (4-6%)	Abnormal AET (>6%)
Concordant SAP/SI positivity	71/178 (40%)	34/89 (38%)	109/221 (49%)
P > .05			
TRs >40	72/178 (40%)	66(89 (74%)	177/221 (80%)
P < .05 for normal AET group vs. inconclusive AET and abnormal AET group			
PSPW index <50%	94/178 (53%)	86/89 (97%)	216 /221(98%)
P < .05 for normal AET group vs. inconclusive AET and abnormal AET group			
MNBI <2000Ω	76/178 (43%)	67/89 (75%)	202/221 (91%)
P < .05 for all pairwise comparisons			
PSPW index <50% and MNBI <2000Ω	49/178 (28%)	65/89 (73%)	199/221 (90%)
P < .05 for all pairwise comparisons			

PPI, proton pump inhibitor; AET, acid exposure time; SAP, symptom association probability; SI, symptom index; TRs, total refluxes; PSPW, post-reflux swallow-induced peristaltic wave; MNBI, mean nocturnal baseline impedance; P value adjusted with Bonferroni correction for multiple comparisons.

Figure legends

Figure 1. ROC curves and area under the curve of impedance-pH metrics obtained comparing 488 patients with PPI-dependent heartburn to 70 healthy controls.

PPI, proton pump inhibitor; AET, acid exposure time; PSPW, post-reflux swallow-induced peristaltic wave; MNBI, mean nocturnal baseline impedance; TRs, total refluxes.

Figure 2. Positivity of impedance parameters in 488 patients with PPI-dependent heartburn as classified according to AET Lyon Consensus thresholds.

PPI, proton pump inhibitor; AET, acid exposure time; SAP, symptom association probability; SI, symptom index; TRs, total refluxes; PSPWI, post-reflux swallow-induced peristaltic wave index; MNBI, mean nocturnal baseline impedance.