Received: 18 May 2023 | Revised: 4 July 2023 | Accepted: 30 August 2023

DOI: 10.1111/nmo.14680

ORIGINAL ARTICLE

Neurogastroenterology & Motility NGM WILEY

Improved diagnosis of reflux hypersensitivity

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Abstract

Background: Reflux hypersensitivity (RH) is characterized by normal esophageal exposure to acid and positive correlation of symptoms to reflux episodes. Positivity of Symptomatic Index (SI) and/or Symptom Association Probability (SAP) is used diagnostically, though experts support that concordance of both is needed. We evaluated differences among patients with RH and concordance of SI/SAP or not.

Methods: Patients with typical reflux symptoms without previous GERD diagnosis, submitted simultaneously to Ph-Impedance off PPI and high resolution manometry were included. Self-response to PPI was evaluated. Patients showing SI and/or SAP positivity were considered having RH and further classified to definite RH if both SI/SAP were positive or indefinite if only one positive.

Key Results: Totally 2659 patients (M/F: 35.6%/64.7%, mean age: 45 ± 14) were included. Final diagnosis was; FH: 21.8%, RH: 29.3% (definite: 14.3%/indefinite: 15%), GERD: 36% and inconclusive GERD: 12.9%. Patients with definite RH showed increased total reflux time, total number of reflux episodes and length of hiatus hernia, and also numerically but not statistically significant increased rates of PPI responsiveness versus indefinite RH and decreased mean nocturnal baseline impedance. Moreover, they showed significantly increased rate of PPI response versus patients with functional heartburn (FH).

Conclusion & Inferences: Some PPI responsiveness is frequent among patients with RH as also with FH, and cannot discriminate those entities clinically when diagnosing RH using SI and/or SAP positive criterion. Patients with RH and SI/SAP concordance differ from patients without. Implementation of a strict RH definition (both SI and SAP positive) can better distinguish RH from FH and should be used in the future.

KEYWORDS
functional heartburn, gastro-esophageal reflux disease, reflux hypersensitivity, symptom associated probability, symptomatic index

1 | INTRODUCTION

Symptoms of reflux can be reported from up to 30% of western world habitants.[1] A significant proportion of such patients will not be finally diagnosed with GERD. After the exclusion of eosinophilic esophagitis and major motility disorders, approximately 1/3 of such patients will be categorized as having reflux hypersensitivity (RH) or functional heartburn (FH) according to the existence or not of a correlation between symptoms and reflux episodes.[2,3] FH and RH are characterized by normal esophageal acid exposure,[4] although, patients with RH show a positive correlation of their symptoms to

reflux episodes and may be benefited by proton pump inhibitor (PPI) therapy.[5] On the contrary, patents with FH have an increased rate of other Functional Gastrointestinal diseases.[6,7]

Previous studies showed that, compared to patients with FH, patients with RH show higher rates of hiatus hernia (HH) existence, acid exposure time (AET), increased total number of refluxes (acid and non-acid) and refluxes with proximal extent. Furthermore, mean nocturnal baseline impedance (MNBI) is lower in RH than in FH.[8,9] The existence of such differences led experts in the field to propose that RH should not be considered as a disorder of brain–gut interaction, but rather one belonging in the spectrum of GERD.[5] There is no clear written consensus on the criteria that should be used in order to diagnose RH.[4,10,11] Some clinicians ask for both SI and SAP positivity, while many studies rely on the positivity of one of them in order to set RH diagnosis.[12–15]

Few studies compared PPI efficacy in RH versus FH.[16-18] Moreover, PPI nonresponsiveness is taken as a diagnostic criterion for FH diagnosis according to the Rome IV criteria.[4] We aimed to assess differences between patients with diagnosis of RH using one or two reflux symptom association parameters and compared them to patients with FH.

Key Points

- Some PPI responsiveness is frequent among patients with RH as also with FH and cannot discriminate those entities clinically.
- Patients with a normal AET and concordance of SI and SAP are a distinct population from patients with SI and SAP discrepancy.
- A strict diagnosis of RH requiring both SI and SAP can better discriminate patients with RH from those having FH.

2 | METHODS

We performed a retrospective analysis of data from patients with long-standing reflux symptoms (heartburn and/or regurgitation) without previous conclusive diagnosis of GERD, who underwent pH-impedance monitoring "off" PPI and high-resolution manometry. Patients with esophageal motility disorder apart from ineffective esophageal motility/absent peristalsis, according to Chicago IV, were excluded, as also patients with previous gastro-esophageal surgeries.[19] Patients were asked to self-report with a 100% scale their response to PPI. Nonresponse to PPI was defined as a self-report of response <50%. PPI response was accessible in 1714 patients.

2.1 | High-resolution manometry–Multichannel intraluminal impedance pH-monitoring protocol

Patients were instructed to stop PPI and histamine H2 blocker for at least 7 days prior to the study. After overnight fast, patients underwent high-resolution manometry (Medtronic). HRM studies were executed by an assembly with a 4.2-mm outer diameter and 36 solid state circumferential pressure sensors spaced at 1-cm intervals (ManoScan; Given Imaging). Studies were performed with patients in the supine position. The manometric protocol included a 30-s baseline recording period to assess the esophago-gastric junction (EGJ) and at least 10 single water swallows (5 mL) at 30-s intervals to evaluate esophageal peristalsis. Data acquisition, display, and analysis were performed using dedicated software (ManoView analytical software; Given Imaging), after appropriate thermal compensation. EGJ anatomic morphology was assessed at the HRM tracing by measuring the distance between distal margin of LES and respiratory induced changes at the CD level. Based on these measurements, the EGJ was categorized following the Lyon Consensus into Type 1, 2, 3 depending on the separation of the crural diaphragm and the LES (1: no separation or up to 1 cm, 2: 1–3 cm, 3 ≥ 3 cm). LOS hypotension was defined as a mean basal LES pressure < 13 mmHg. MII-pH monitoring was performed as follows: the MII-pH catheter (Diversatek Healthcare for studies executed before 2018) or OMON (Jinshan Science and Technology, Chongqing, China for studies executed after 2018) was placed with a proximal pH sensor at 5 cm above the LES and distal pH sensor in the stomach. The catheter has six impedance pairs of electrodes at 3, 5, 7, 9, 15, and 17 cm above the LES. We analyzed the MII-pH tracings using the dedicated software and visual editing based on our standard protocol. Only pH-impedance studies in which the probe remained in place for at least 16 h were considered valid for analysis. The patients were instructed to complete a diary that included indications of the beginning and ending times of meals and changes in body position and were asked to report in the same diary the exact time whenever they experienced reflux symptom as also the type of symptom. AET was calculated as the percentage of time during which the pH was below four at the esophageal pH sensor.

Number of reflux episodes (NRE) and reflux-symptom association (symptom index—SI and symptom association probability—SAP) were documented. The SI and SAP were calculated and designated as positive when SI > 50% or SAP > 95%. SI and SAP were evaluated only if the patient reported more than three symptoms as also if more than eight reflux episodes were documented during the study. The OMON software provided automatic analysis of MNBI using the simplified method described by our group that is, a mean baseline impedance value over the whole supine period.[20] MNBI was assessable in 350 patients GERD diagnosis was made by using Lyon consensus criteria for 24 h pH-Impedance. Patents with an AET (off-PPI) >6% were considered to have GERD, 4%–6% inconclusive GERD and <4% definitely not GERD. Patients with an AET <4% showing either SI and/or SAP positivity were considered having RH and further categorized to definite RH if both SI and SAP were positive and to indefinite RH if only one of them was positive. Patients with AET <4% and both SI and SAP negative were considered as having FH. Patients with an AET: 4%–6% were considered as patients with indefinite GERD.

Since this study was a post hoc analysis of de-identified previously collected data from esophageal studies with no direct link to individual patients, formal ethics approval was not deemed to be necessary.

2.2 | Statistical analysis

Statistical analysis was performed by using SPSS V23 (SPSS software; SPSS Inc). Data were expressed as frequencies, mean ± standard deviation (SD), or median (interquartile range, [IQR]), as appropriate. Quantitative variables were compared between groups by using Student's *t*-test or the Mann–Whitney test for normally distributed and non-normally distributed variables, respectively. Qualitative variables were compared by using the chi-squared test or Fisher's exact test, as appropriate. Comparisons between groups were done separately in pairs, by using the chi-squared test as appropriate. All tests were 2-sided and $p < 0.05$ were considered to be significant.

3 | RESULTS

In total 2659 patients (M/F: 35.6%/64.7%, mean age: 45 ± 14) were included in the study. Among them 580 (21.8%) were diagnosed with FH and 779 (29.3%) with RH (definite: 399 [15%], indefinite: 380 [14.3%]) while 343 (12.9%) were diagnosed with inconclusive GERD and 957 (36%) with conclusive GERD.

3.1 | RH (definite and indefinite) versus FH

Compared to patients with FH, patients with RH showed higher total AET, upright AET but not supine AET; higher total number of refluxes (acid and nonacid) and number of episodes with proximal extent. They also showed lower mean distal contractile integral (DCI) and increased rate of EGJ type 2 and 3. RH patients had numerically increased rates of LES hypotension and rate of ineffective esophageal motility/absent peristalsis. MNBI (accessible in 216 patients) was not significantly lower than in patients with FH. The PPI responsiveness among patients with RH was not statistically different compared to patients with FH Table 1.

3.2 | Indefinite RH versus FH

There were no significant differences between patients with indefinite RH and FH concerning; AET ($p = 0.213$) total number of refluxes ($p = 0.483$) as also acid and nonacid reflux episodes, number of episodes with proximal extent ($p = 0.798$), rate of EGJ type 2 and 3($p = 0.471$), LES hypotension, ineffective esophageal motility/absent peristalsis diagnosis as also length of HH and PPI response ($p = 0.386$), mean DCI and mean MNBI ($p = 0.901$).

3.3 | Definite versus indefinite RH

Patients with definite RH in comparison to patient with indefinite RH showed significantly increased total AET as also total number of refluxes, acid and nonacid reflux episodes and number of episodes with proximal extent. They also showed significantly increased rate of EGJ type 2 and 3 and length of HH. They also showed numerically but not in a statistically significant way increased upright reflux time and supine reflux time, increased rates of LES hypotension, rate of ineffective esophageal motility/absent peristalsis diagnosis as also

TABLE 1 Comparison of characteristics of patients with functional heartburn versus reflux hypersensitivity.

	Functional heartburn	Reflux hypersensitivity	*p*
Total AET (%)	1.12 ± 0.94	1.65 ± 0.96	<0.001
Upright AET (%)	1.88 ± 5.10	3.49 ± 9.53	0.03
Supine AET (%)	0.73 ± 4.18	1.36 ± 8.09	0.165
Total reflux number	26 ± 19	42 ± 24	<0.001
Acid reflux number	11 ± 10	32 ± 15	<0.001
Non-acid reflux number	14 ± 12	20 ± 16	<0.001
Number of episodes with proximal extent	13 ± 12	24 ± 17	<0.001
MNBI (3 cm)	2016.1 ± 1066.2	1872.1 ± 608.7	0.893
Length of Hiatus Hernia (cm)	0.47 ± 0.95	0.57 ± 0.97	0.101
EGJ type 2 and 3	20.9%	27.1%	0.043
Mean DCI	1061.9 ± 1039.6	904.9 ± 898.3	0.015
Rate of low LES pressure	42.5%	47.2%	0.165
Rate of diagnosis of ineffective esophageal motility/absent contractility (%)	33.8%	38.2%	0.170
PPI responsiveness	(137/330) 41.5%	(223/468)47.6%	0.168

Note: Numerical values expressed as mean ± SD. EGJ type 2: separation of LES to CD 1–3 cm, EGJ type 3: separation of LES to CD >3 cm.

TABLE 2 Comparison of characteristics of patients with indefinite versus definite reflux hypersensitivity.

	Indefinite reflux hypersensitivity	Definite reflux hypersensitivity	*p*
Total AET	1.36 ± 1.09	1.85 ± 1.13	<0.001
Upright AET	3.04 ± 0.93	3.60 ± 0.87	0.388
Supine AET	1.19 ± 0.69	1.47 ± 0.86	0.624
Total reflux number	32 ± 19	50 ± 29	<0.001
Acid reflux number	16 ± 12	25 ± 15	<0.001
Non-acid reflux number	16 ± 13	24 ± 24	<0.001
Rate of episodes with proximal extent (%)	16.1 ± 13.2	28.7 ± 18.4	<0.001
MNBI (3 cm)	1959 ± 1515	1774.7 ± 498.9	0.483
Length of Hiatus Hernia (cm)	0.48 ± 0.90	0.64 ± 1.03	0.021
EGJ type 2 and 3	22.9%	31.1%	<0.001
Mean DCI	921.3 ± 900.8	925.6 ± 887.9	0.947
Rate of low LES pressure	45.8%	47.9%	0.305
Rate of diagnosis of ineffective esophageal motility/absent contractility	34.2%	38.6%	0.207
PPI responsiveness	104/229 (45.4%)	119/239 (49.8%)	0.356

Note: Numerical values expressed as mean ± SD. EGJ type 2: separation of LES to CD 1–3 cm, EGJ type 3: separation of LES to CD >3 cm.

mean DCI, mean MNBI and PPI responsiveness. (Table 2) Moreover patients with definite RH showed increased rates of PPI response when compared to patients with FH ($p = 0.031$) Figure 1.

3.4 | SI positivity versus SAP positivity

When comparing patients with only SAP positivity ($n = 284$) versus only SI positivity ($n = 95$) they showed increased AET (1.28 ± 1.05% vs. 1.59 ± 1.16%, $p = 0.015$) but decreased total reflux number (28 ± 15 vs. 45 ± 24, $p < 0.001$). No differences among manometric findings were found (LES Hypotension, diagnosis of IEM/absent peristalsis, rate of EGJ type 2/3—$p = 0.342$, 0.214, and 1.000, respectively). Moreover, no difference as far as PPI responsiveness was concerned was found (43.9% vs. 51.7%, $p = 0.360$) (Table 3).

3.5 | Definite RH versus inconclusive GERD

Patients with inconclusive GERD in comparison to patient with definite RH showed increased total AET (in the upright and supine position), number of acid refluxes but not total NRE or episodes with proximal extent and decreased rate of nonacid reflux episodes. Rate of EGJ type 2 and 3, length of HH, rates of LES hypotension, rate of ineffective esophageal motility/absent peristalsis diagnosis as also mean DCI and PPI responsiveness did not differ among patients with inconclusive GERD to patients with definite RH. The MNBI was significantly lower in patients with inconclusive GERD versus definite RH (difference also significant [$p < 0.001$] when comparing patients with inconclusive vs. conclusive GERD; Table 4; Figures 2 and 3).

4 | DISCUSSION

Patients with RH consist a significant portion of patients with reflux symptoms and is a heterogeneous population with respect to Ph-Impedance, manometric characteristic and response to different treatments. The significance of our study is that we tried to further classify patients with RH by discriminating them according to the concordance of symptomatic index and symptom associated probability. We observed that patients with both SI and SAP positivity showed increased total acid exposure, proximal total reflux events, distal total reflux events and EGJ type 2 and 3, in comparison to patients with only SI or SAP positive. Moreover, patients with both SI and SAP positive when compared to patients with AET in the gray area of 4–6, showed no difference as to proximal total reflux events, distal total reflux events, EGJ type 2 and 3 and the rate of manometric findings supportive of GERD as LES hypotension and diagnosis of ineffective esophageal motility or absent contractility. On the contrary, patients showing disagreement between SI and SAP positivity (only one positive), even if subtle numerical differences existed, did not show statistical significant differences in all the evaluated metrics when compared to patients with FH. These findings indicate that patients with indefinite RH show characteristics similar to FH and therefore have a disorder of brain–gut interaction while patients with definite RH share most common characteristics to patients with indefinite GERD and should be regarded as patients having a disorder of the spectrum of reflux disease.

We showed once more that patients with a conventional RH diagnosis (SI and/or SAP positive) show significantly increased total acid exposure time, proximal total reflux events, total reflux events,

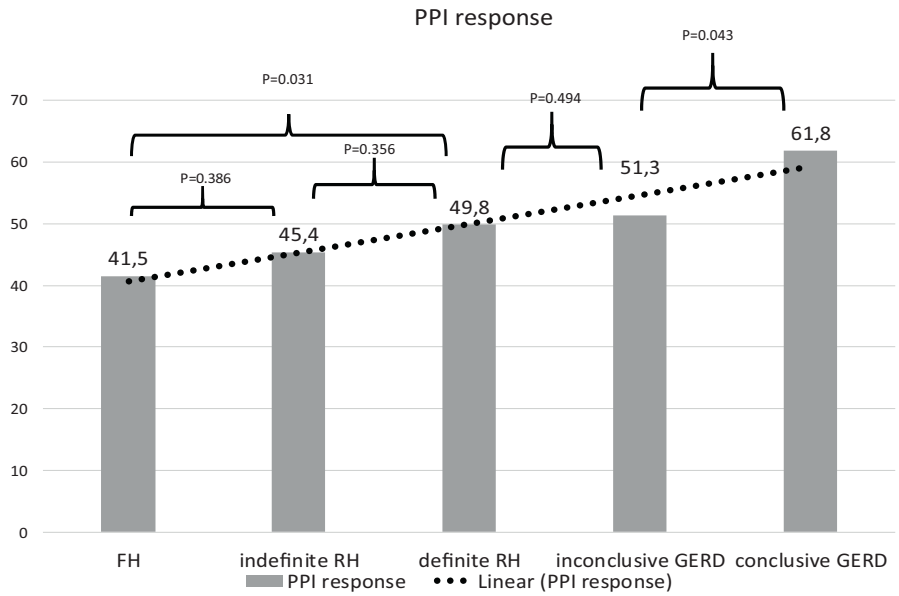

FIGURE 1 Response to PPI according to diagnosis.

TABLE 3 Comparison of characteristics of patients with RH showing only SI positivity versus patients with RH showing only SAP positivity

	Only SAP positivity	Only SI positivity	*p*
Total AET (%)	1.28 ± 1.05	1.59 ± 1.16	0.015
Total reflux number	28 ± 15	45 ± 24	<0.001
EGJ type 2 and 3	31.3%	31.3%	1.000
Rate of low LES pressure	47.8%	46.5%	0.342
Rate of diagnosis of ineffective esophageal motility/absent contractility	40.9%	38.1%	0.214
PPI responsiveness	43.9%	51.7%	0.360

and rate of EGJ type 2 and 3 in comparison to patients with FH. Previously published studies have proven that patients with FH and RH have discrete characteristics. Patients with FH have esophageal mucosal innervation pattern similar to controls, while do not show increased levels of e-cadherins in the serum as patients with GERD do.[21,22] Moreover, patients with FH do not show microscopic signs of esophagitis in comparison to patients with RH who also show pronouncedly disturbed pH impedance and HRM metrics comparing to FH, though obviously in a lesser way than in patients with GERD.[8,9,23,24]

Additionally, we assessed differences in self-report response to PPI treatment among patients with FH and RH. Previous studies have showed that patients with RH, also show some degree of response to PPIs even in a scale much lower than patients with GERD though the data are scarce.[4,15,16] They also show some response to pain modulators as patients with FH do, but on the contrary may also respond to anti-reflux surgery[14,25,26] while recent data have proven that baclofen can ameliorate symptoms among patients with RH as it reduces the frequency of reflux events and inhibits TLESR.[27,28] We observed that some PPI responsiveness is frequently reported by both patients (with RH as also FH) and cannot be used to discriminate those entities clinically. Previous studies have reported a significant rate of responsiveness to PPI among patients with FH which was calculated up to 44%, a rate very similar to ours.[17,18] Once more, PPI response gradually increased moving from patients with FH towards patients with conclusive GERD. It must be underlined that patients with concordance of SI and SAP reported significantly increased rates of PPI response in comparison to patients with FH and similar to patients with indefinite GERD, a fact not observed when comparing patients with SI and SAP disagreement, among whom the rate of self-reported PPI response was similar to patients with FH. Additionally, no differences were noted when comparing patients with only SAP versus only SI positivity even if increased numerical rates were found among patients with only SI positivity. Therefore, favoring one over another metric cannot tailor a clinical decision as far as future response to PPIs in patients with RH is concerned. Originally, it was supported that SAP outperforms SI in documenting a correlation between symptoms and reflux episodes, though recent reports have pointed out that SAP is an imperfect metric in distinguishing FH from RH and in predicting response to anti-reflux surgery in patients with RH.[29,30] It must also be stated that the population of patients showing only SAP positivity was three times larger than patients with only SI in our study, possibly making it not such a selective metric.

It is of special importance also to stress out the role of the clinician during pH-impedance study analysis. It is well-known that automated analysis of pH-impedance monitoring overestimates nonacid reflux episodes.[31] Moreover, recent data showed that significant variability between automated analysis and expert interpretation exists as far as reflux episode in general and post-reflux swallow-induced peristaltic wave (PSPW) identification is concerned. The use of well-predefined definitions proposed by the Wingate Consensus improved the agreement, variability, and reliability of reflux episode

	Indefinite GERD	Definite reflux hypersensitivity	p
Total AET (%)	4.87 ± 0.57	1.85 ± 1.13	<0.001
Upright AET (%)	6.47 ± 5.11	3.60 ± 0.87	<0.001
Supine AET (%)	3.17 ± 4.19	1.47 ± 0.86	<0.001
Total reflux number	51 ± 32	50 ± 29	0.544
Acid reflux number	31 ± 18	25 ± 15	<0.001
Non-acid reflux number	18 ± 20	24 ± 24	<0.001
Rate of episodes with proximal extent	29.2 ± 23.1	28.7 ± 18.4	0.782
MNBI (3 cm)	1332.9 ± 591.9	1774.7 ± 498.9	0.001
Length of Hiatus Hernia	0.77 ± 1.13	0.64 ± 1.03	0.140
EGJ type 2 and 3	31.5%	31.1%	0.937
Mean DCI	969.2 ± 1140.5	925.6 ± 887.9	0.569
Rate of low LES pressure	48.7%	47.9%	0.826
Rate of diagnosis of ineffective esophageal motility/absent contractility	41.4%	38.6%	0.241
PPI responsiveness	100/187 (53.5%)	119/239(49.8%)	0.494

Note: Numerical values expressed as mean ± SD. EGJ type 2: separation of LES to CD 1–3 cm, EGJ type 3: separation of LES to CD >3 cm.

TABLE 4 Comparison of characteristics of patients with indefinite GERD versus definite reflux hypersensitivity.

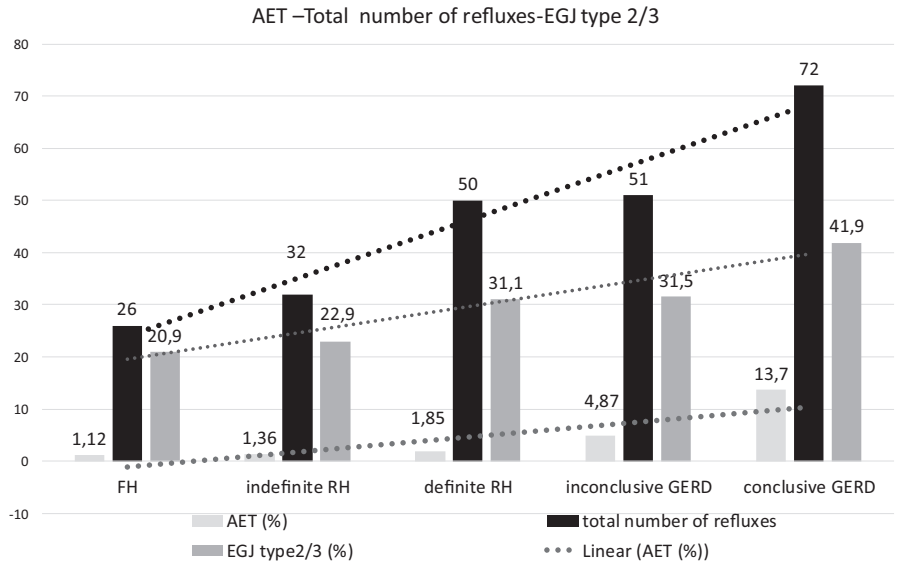

FIGURE 2 Acid exposure time (AET), total number of refluxes and rate of esophago-gastric junction (EGJ) type 2/3 according to diagnosis.

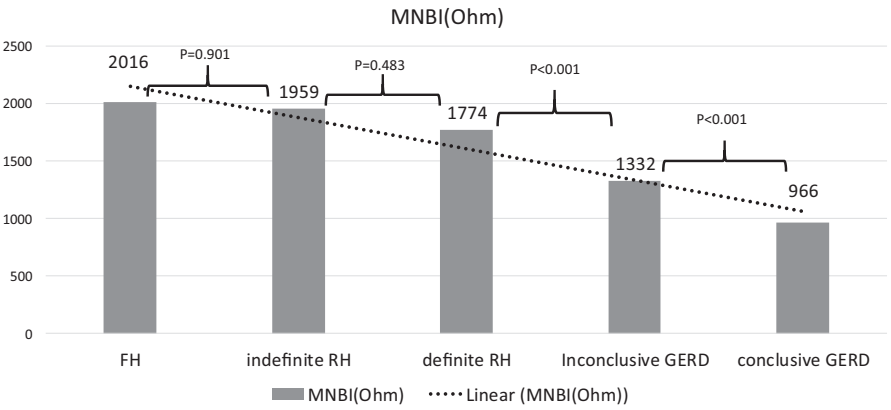

FIGURE 3 Mean nocturnal baseline impedance at 3 cm over lower esophageal sphincter according to diagnosis.

and PSPW identification.[32] Therefore, we once more stress out the fact that careful visual analysis of the MII pH studies, particularly on the reflux events identification and the symptoms markers editing is needed. Both the incorrect identification of reflux episodes, and patients' hyper-vigilance leading them initially to over-document symptoms, may lead to incorrect calculation of SI and SAP with further consequences on patients' final diagnosis.

We also validated previous results proving that MNBI can discriminate patients with RH and FH from patients with GERD. Significantly different MNBI values were also noted when comparing patients with inconclusive GERD to patients with both SI and SAP positivity but negative AET (defined by us as patients with definite RH).[22,33]

4.1 | Study limitations

Our study is based on a retrospective analysis of motility and reflux monitoring in patients with persistent typical GERD symptoms submitted to upper physiology testing for diagnostic purposes. We do not present endoscopic data as these were not available across all patients. Since we did not include any patient with a study on-PPI, or patients submitted to the studies presurgically, or with previous Barrett's diagnosis, no patient with definite endoscopic GERD diagnosis was most possibly included in our study. Additionally, PPI response was assessed by a non-validated questionnaire already imported in our standard pre-procedural protocol. Therefore, a randomized prospective trial is needed in order to properly evaluate different treatment strategies in RH after implementing a strict RH diagnosis as proposed by our study (including PPIs).

5 | CONCLUSION

Patients with RH consist a large portion of patients with typical reflux symptoms. According to our study patients with typical reflux symptoms and concordance of SI and SAP positivity are a different population from patients with typical reflux symptoms and either SAP or SI positivity. A strict diagnosis of RH requiring both SI and SAP positivity can better discriminate patients with RH as far as patients with typical reflux symptoms are concerned from those having FH on two grounds: clinically and on the basis of HRM and pH-impedance studies' findings. Such a criterion should be used in the future to discriminate patients, and to tailor therapeutic management of RH patients.

AUTHOR CONTRIBUTIONS

Theodoros Voulgaris involved in data collection, analysis, manuscript preparation, and review; Shintaro Hoshino involved in data collection; Daniel Sifrim involved in study concept and design, and manuscript critical review; Etsuro Yazaki and Daniel Sifrim involved in study concept and design, manuscript preparation, and critical review. All authors approved the final version of the manuscript.

FUNDING INFORMATION

Grant support: None declared.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Voulgaris T, Hoshino S, Sifrim D, Yazaki E. Improved diagnosis of reflux hypersensitivity. *Neurogastroenterology & Motility*. 2023;00:e14680. doi:10.1111/nmo.14680