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ALIMENTARY TRACT

Identification of Different Phenotypes of Esophageal Reflux Hypersensitivity and Implications for Treatment

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BACKGROUND & AIMS: **Reflux hypersensitivity (RH), a functional esophageal disorder, is detected in 14%–20% of patients who present with typical esophageal symptoms. As many as 40% of patients with RH do not respond to treatment with pain modulators or proton pump inhibitors (PPIs); behavior disorders might contribute to lack of treatment efficacy. We aimed to assess the prevalence of behavioral disorders and their effects on typical reflux symptoms in patients with RH.**

METHODS: **We performed a retrospective study of 542 patients with PPI-refractory esophageal symptoms (heartburn, regurgitation, or chest pain) or with symptoms that responded to PPI therapy, evaluated for anti-reflux surgery from January 2016 through August 2019 at a single center in London, United Kingdom. We collected data on symptoms, motility, and impedance-pH monitoring and assigned patients to categories of RH (n = 116), functional heartburn (n = 126), or non-erosive reflux disease (n = 300).**

RESULTS: **Of the 116 patients with a diagnosis of RH, 59 had only hypersensitivity, whereas 57 patients (49.2%) had either excessive supragastric belching (SGB, 39.7%), based on 24-hour impedance-pH monitoring, or rumination (9.5%), based on postprandial manometry combined with impedance. The prevalence of SGB and rumination in patients with RH was significantly higher than in patients with functional heartburn (22%; $P < .001$). Patients with RH and rumination were significantly younger ($P = .005$) and had the largest number of non-acid reflux episodes ($P = .023$). In patients with RH with SGB, SGB episodes were associated with 40.6% of marked reflux symptoms (heartburn, regurgitation, or chest pain), based on impedance-pH monitoring. In patients with RH and rumination, 40% of reflux-related symptoms (mostly regurgitation) were due to possible rumination episodes.**

CONCLUSIONS: **Almost half of patients with a diagnosis of RH have behavior disorders, including excessive SGB or rumination. Episodes of SGB or rumination are associated with typical reflux symptoms. Segregation of patients with diagnosis of RH into those with vs without behavioral disorders might have important therapeutic implications.**

Keywords: NERD; FH; Psychologic; Pain Perception.

Gastroesophageal reflux disease (GERD) is defined as reflux of gastric contents causing troublesome symptoms and/or complications.[1] On the basis of symptom profile, endoscopic findings, and distinct patterns on ambulatory reflux monitoring, patients with reflux symptoms can be phenotyped into erosive reflux disease, non-erosive reflux disease (NERD), reflux hypersensitivity (RH), and functional heartburn (FH).

Hypersensitivity to acid reflux episodes on ambulatory pH monitoring was described many years ago,[2] which has expanded to identification of hypersensitivity to non-acid reflux episodes with impedance-pH

Abbreviations used in this paper: **AET, acid exposure time; CI, confidence interval; EGJ, esophagogastric junction; FH, functional heartburn; GERD, gastroesophageal reflux disease; HRM, high-resolution manometry; HRM/Z, HRM combined with impedance; LES, lower esophageal sphincter; MNBI, mean nocturnal baseline impedance; NERD, non-erosive reflux disease; OR, odds ratio; PPI, proton pump inhibitor; RH, reflux hypersensitivity; RH-RUM, reflux hypersensitivity with rumination; RSA, reflux symptom association; SAP, symptom association probability; SGB, supragastric belching; SI, symptom index.**

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monitoring.[3] According to Rome IV criteria, the diagnosis of RH requires (1) occurrence of heartburn or chest pain, (2) normal endoscopy, (3) absence of major esophageal motility disorders, and (4) normal acid esophageal exposure but positive reflux symptom association (RSA).[4] In patients evaluated for heartburn, RH has a prevalence of around 14%.[5] Taking into account the ~28% prevalence of GERD,[6] the prevalence of RH is significant, especially in proton pump inhibitor (PPI)-refractory patients.[7–9]

Because RH symptoms are time-related to reflux episodes, treatment recommendations include increasing acid suppression[7,10] and modulation of pain perception,[4] but approximately 40% remain refractory to these approaches.[9,11,12] Although the reason for refractoriness is not completely understood, psychological and behavioral disturbances are increasingly recognized within esophageal disorders.[13] For example, a significant proportion of PPI-refractory patients have postprandial rumination or increased supragastric belching (SGB),[14–16] which do not respond to PPIs or pain modulators.[17,18] We hypothesized that undiagnosed behavioral disorders might contribute to treatment failure in RH patients. The aim of this study was to reassess symptom profiles and impedance pH tracings in a large cohort of RH patients to evaluate for behavioral disorders.

What You Need to Know

Background

Many patients with reflux hypersensitivity do not respond to treatment with pain modulators or proton pump inhibitors; behavior disorders might contribute to lack of treatment efficacy.

Findings

Almost half of patients with a diagnosis of reflux hypersensitivity have behavior disorders, including excessive supragastric belching or rumination, which are associated with typical reflux symptoms.

Implications for patient care

Patients with reflux hypersensitivity and behavior disorders might require different therapeutic strategies than patients without behavior disorders.

Methods

Study Subjects

We identified patients with PPI-refractory esophageal symptoms (heartburn, regurgitation, or chest pain) or PPI-responsive patients evaluated for antireflux surgery by interrogating the electronic database (January 2016–August 2019) at the Royal London Hospital GI Physiology Unit. Patients were included if they were older than 16 years and underwent high-resolution manometry (HRM) and off-PPI impedance-pH monitoring. Patients were excluded if they had (1) endoscopic esophagitis, Barrett's esophagus, or eosinophilic esophagitis, (2) HRM diagnosis of major esophageal motility disorders, or (3) belching as the main symptom. Medication use and prior foregut surgery were not exclusionary. Consequently, 10 patients with persistent symptoms on antidepressants (citalopram and gabapentin [n = 1], gabapentin [n = 2], citalopram [n = 2], amitriptyline [n = 2], nortriptyline [n = 1], venlafaxine [n = 1], and sertraline [n = 1]), opioids (n = 9), prior antireflux surgery (n = 4), and prior bariatric surgery (n = 1, sleeve gastrectomy) were included in the RH group.

Using Lyon consensus acid exposure time (AET) thresholds,[19] we divided patients into those with normal AET (<4%) and pathologic AET (>6%). For clarity of interpretation, patients with borderline AET (4%–6%) were excluded from the analysis. To reliably evaluate RSA, patients were included only if they had ≥3 GERD symptoms during impedance-pH monitoring; RSA required both symptom index (SI) and symptom association probability (SAP) to be positive.[19,20]

For this retrospective analysis of clinically indicated tests with no identifiable patient data, formal ethics approval was not deemed necessary, but we obtained approval from our Quality and Service Improvement department at the Royal London Hospital.

Questionnaire, High-Resolution Manometry, and Ambulatory Impedance-pH Monitoring

As per our clinical routine, all patients completed the Reflux Disease Questionnaire[21] before HRM testing.

HRM (Sandhill Scientific, Highlands Ranch, CO, or ManoScan, Medtronic, Minneapolis, MN) and impedance-pH monitoring (Sandhill Scientific, or OMOM System, Jinshan Science and Technology, Chongqing, China) were performed after overnight fasting. An HRM catheter with 36 solid-state pressure sensors spaced 1 cm apart was inserted transnasally to record pressures from the stomach to the upper esophageal sphincter. After catheter placement and identification of the lower esophageal sphincter (LES), a 30-second baseline recording and ten 5-mL water swallows were performed in the right lateral position to assess esophageal motility. When rumination was suspected on medical interview, HRM combined with impedance (HRM/Z) (Sandhill Scientific) was performed with postprandial evaluation for at least 15 minutes.

Ambulatory impedance-pH monitoring was performed off-PPI after HRM or HRM/Z, with PPIs and/or H_2 receptor antagonists discontinued for at least 7 days. The impedance-pH catheter was inserted with the esophageal pH sensor positioned 5 cm above the LES, and 6 impedance channels positioned 3, 5, 7, 9, 15, and

17 cm above the LES, respectively, and connected to a portable recorder.

Data Analysis

HRM and impedance-pH monitoring studies were reanalyzed and manually edited by using ManoView 3.0 (Medtronic), Bioview Analysis (Sandhill Scientific), and/or OMOM Analysis (Jinshan Science and Technology) specifically for the purpose of this study.

High-resolution manometry. Major motility disorders on HRM included achalasia, esophagogastric junction (EGJ) outflow obstruction, distal esophageal spasm, hypercontractile esophagus, and absent contractility and were assessed by using Chicago classification v3.0.[22] EGJ morphology and EGJ-contractile integral were analyzed as recently described.[23]

Ambulatory impedance-pH monitoring. Automated analysis of impedance-pH tracings was followed by manual editing of reflux episodes using published criteria[24] and measurement of mean nocturnal baseline impedance (MNBI).[25]

Reflux symptom association. Symptoms occurring within 2 minutes after onset of reflux were considered associated with the reflux episode (symptomatic reflux). SI and SAP were used to assess RSA.[26,27] SI measures the proportion of symptoms associated with reflux episodes during the 24-hour recording and is positive when $\geq$50%. SAP evaluates if reflux episodes and symptoms co-occurred purely by chance by assessing for the presence or absence of reflux and/or symptoms for each 2-minute segment of the ambulatory reflux study. Using a Fisher exact test on these data, $P < .05$ indicates the probability of chance association is <5%, corresponding to a positive SAP (>95%).

Definitions of Non-erosive Reflux Disease, Reflux Hypersensitivity, and Functional Heartburn

NERD, RH, and FH were defined by using Rome IV criteria.[4] Although originally intended only for heartburn and chest pain, we adapted RH criteria to include regurgitation, because the Montreal definition describes regurgitation as a typical GERD symptom,[1] and several RH studies have similarly included regurgitation.[9,11,12]

All patients had normal endoscopy. NERD was diagnosed when AET was >6% regardless of RSA, RH required AET <4% with positive RSA, whereas FH required AET <4% with negative RSA.

Definitions of Supragastric Belching and Rumination

SGBs were identified on impedance-pH monitoring by using previously described criteria,[28] consisting of an abrupt $\geq$1000 Ω antegrade rise in impedance, followed by retrograde recovery to baseline. Liquid reflux episodes occurring within 1 second after SGB defined SGB-induced reflux. On the basis of our previous analysis of prevalence of SGB in healthy asymptomatic subjects, >13 SGB episodes/24 hours were considered pathologic.[29]

Rumination was diagnosed by using HRM/Z as previously described.[30] On the basis of HRM/Z findings, a patient was considered a ruminator even in the presence of SGB on impedance-pH monitoring. A rumination episode was defined as impedance-detected retrograde gastroesophageal liquid flow reaching the proximal esophagus, which is associated with a rapid gastric pressure increase (>30 mm Hg). Rumination was characterized using HRM/Z as follows: (1) primary rumination: rumination after abdominal pressure increase; (2) secondary rumination: rumination occurring during spontaneous gastroesophageal reflux; and (3) SGB-associated rumination: rumination after SGB.[30]

Relationship Between Supragastric Belching or Possible Rumination Episodes and Gastroesophageal Reflux Disease Symptoms During Impedance-pH Monitoring

In patients with RH, we analyzed the association between SGB or possible rumination episodes and GERD symptoms (ie, heartburn, regurgitation, or chest pain). We considered a GERD symptom to be triggered by SGB if marked by the patient within 20 seconds after SGB. We selected a short time window because we expected very rapid perception of SGB-induced esophageal distention. Three patterns were identified: (1) symptom associated with SGB without liquid reflux (Figure 1*A*); (2) symptom associated with SGB-induced reflux (Figure 1*B*); and (3) symptom associated with SGB occurring during reflux (Figure 1*C*).

Non-acid reflux episodes with high proximal extent (reaching the most proximal impedance channel, 17 cm above LES) within the first postprandial hour were regarded as possible rumination episodes.[15] We calculated the proportion of early postprandial GERD symptoms that could be considered possible rumination episodes. In type 3 rumination, SGB-induced reflux with high proximal extent occurring outside 1-hour postprandial periods was also included in the calculation.

Statistical Analysis

Continuous variables are expressed as median (interquartile), and categorical variables are expressed as numbers (percent). Overall differences across 3 groups were assessed by using the Kruskal-Wallis test for continuous variables or Fisher exact test for categorical variables. Mann-Whitney test and Fisher exact test were used to compare between each pair of the 3 groups. To allow for multiple testing within each variable, the *P* values from the pairwise comparisons were

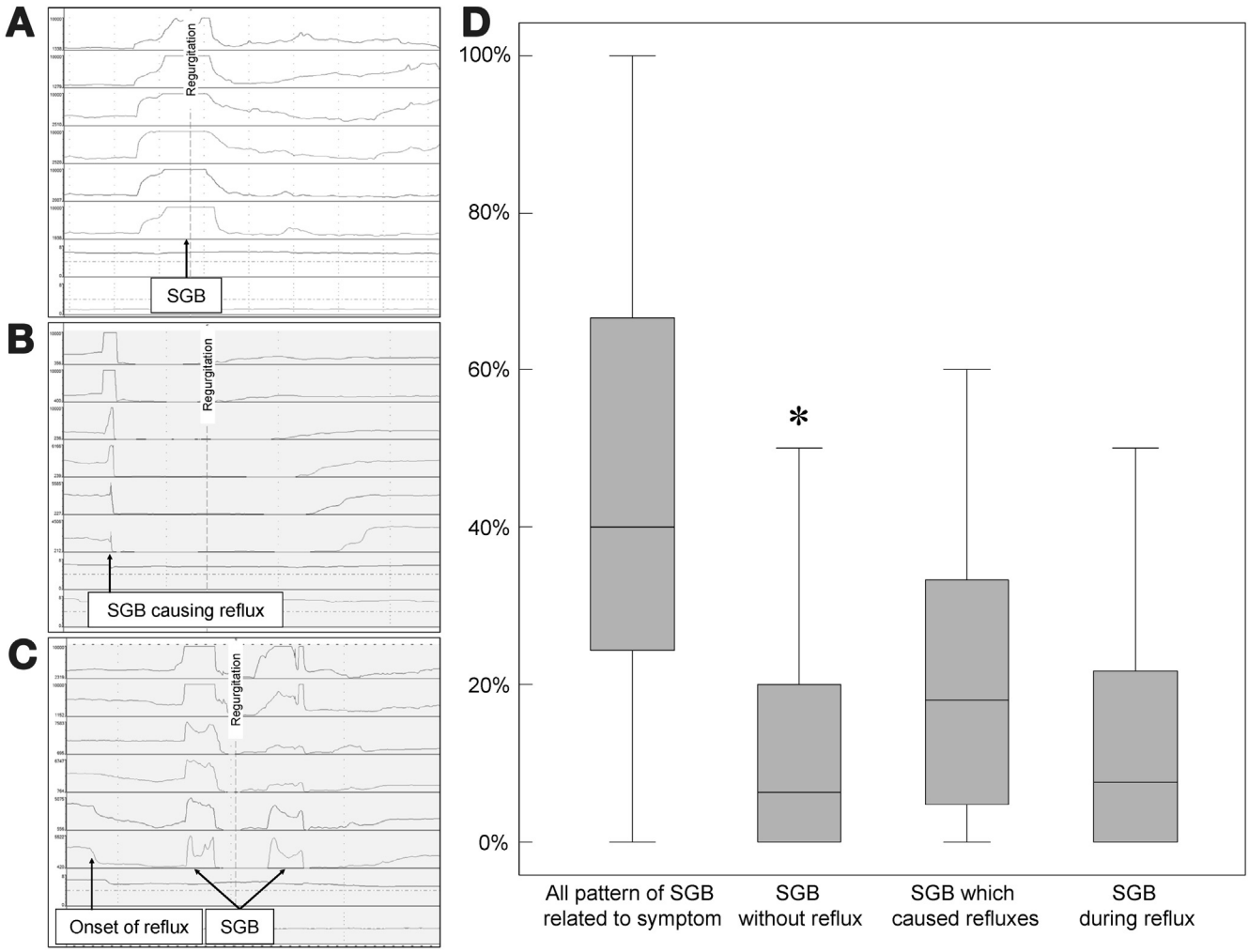

Figure 1. Association between SGB and GERD symptoms. During impedance-pH monitoring, GERD symptoms were marked within 20 seconds after SGB without liquid reflux (*A*), SGB causing reflux (*B*), or SGB during liquid reflux (*C*). SGB was associated with 40.5% (24.5%–66.7%) of GERD symptoms (*D*). GERD, gastroesophageal reflux disease; SGB, supragastric belching. *$P = .022$ compared with SGB that caused refluxes.

given a Bonferroni adjustment. Univariate logistic regression was performed to identify predictors of SGB or rumination in patients with RH, using odds ratios (ORs) and 95% confidence interval (CI) for predictors identified on univariate analysis, followed by multivariate analysis using predictors with $P < .20$ on univariate analysis. All analyses were performed by using R software, version 3.3.1 (R Core Team, Vienna, Austria). P value $< .05$ was considered statistically significant.

Results

Patients

Of 597 patients, 55 were excluded (38 had a major motility disorder, 10 had technical problems with impedance-pH tracings, and 7 had very low MNBI [<1000 ohms] from significantly impaired mucosal integrity). The final study cohort included 116 patients with RH, 126 patients with FH, and 300 patients with NERD. Demographics and clinical characteristics are described in Supplementary Table 1.

Prevalence of Supragastric Belching and Rumination

The proportion of patients with excessive SGB in the RH group (39.7%) was significantly higher than in the FH group (22%; $P = .01$) and similar to the NERD group (37.7%; $P = 1$). On the other hand, rumination was detected on HRM/Z in 11 patients (9.5%) with RH, which was significantly higher than in FH (0 [0%]; $P < .001$) or NERD groups (4 [1.3%]; $P < .001$). Taken together, the proportion of patients with excessive SGB or rumination was 49.2% in RH, 22% in FH, and 39% in NERD (Figure 2).

Clinical Characteristics of Reflux Hypersensitivity Patients

Within the 116 patients with initial diagnosis of RH, we identified 3 phenotypes: (1) 59 patients (51%) with

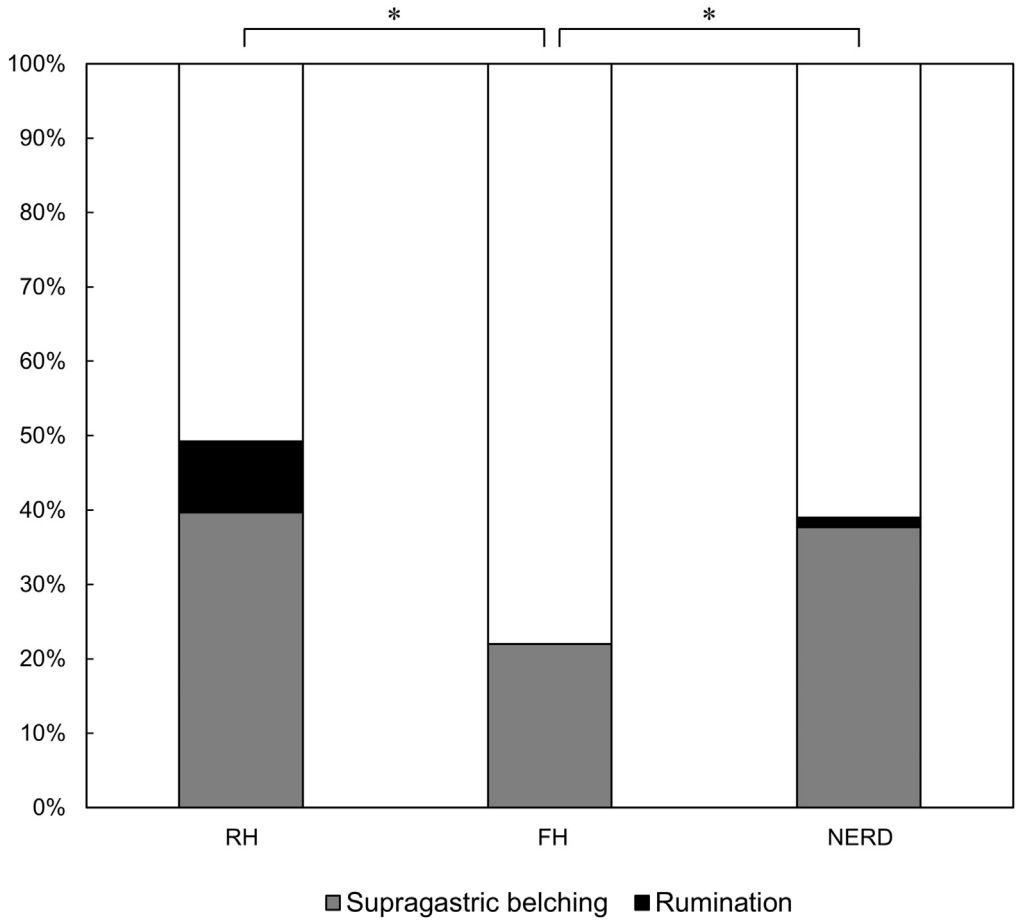

Figure 2. Proportion of patients with excessive supragastric belching during impedance-pH monitoring and with rumination during postprandial high-resolution manometry combined with impedance in RH, FH, and NERD. FH, functional heartburn; NERD, non-erosive reflux disease; RH, reflux hypersensitivity. *$P < .01$.

"pure" RH (RH-pure), (2) 46 patients (40%) with excessive SGB (RH-SGB), and (3) 11 patients (9%) with rumination (RH-RUM) confirmed by HRM/Z (Table 1). Patients with RH-RUM were significantly younger than the other phenotypes ($P = .005$). Proportions of heartburn and regurgitation were similar in patients with RH-

Table 1. Clinical Characteristics of the 3 RH Groups

	Pure reflux hypersensitivity (RH-pure) (N = 59)	Supragastric belching (RH-SGB) (N = 46)	Rumination (RH-RUM) (N = 11)	*P* value
Age (*y*)	42 (33–54)	40 (30–51)	22 (20–34)[a,b]	.005
Female (n, %)	47 (77.0)	27 (57.4)	9 (81.8)	.059
BMI (kg/m^2)	28.0 (24.0–30.0)	26.0 (21.8–28.0)	22.0 (20.5–27.4)	.054
RDQ	11 (10–12)	10 (8–12)	10 (6–12)	.524
No. of patients having each symptom with positive SI and SAP				
Heartburn (n, %)	15 (25.4)	18 (39.1)	0 (0.0)[b]	.019
Regurgitation (n, %)	28 (47.5)	20 (42.6)	8 (72.7)	.196
Chest pain (n, %)	1 (1.7)	1 (2.2)	0 (0.0)	.883
Heartburn and regurgitation (n, %)	13 (22.0)	7 (15.2)	3 (27.3)	.555
Regurgitation and chest pain (n, %)	1 (1.7)	0	0	.614
All 3 symptoms (n, %)	1 (1.7)	0	0	.614

NOTE. Percentages in parentheses relate to each column.
BMI, body mass index; RDQ, Reflux Disease Questionnaire; RH, reflux hypersensitivity; SAP, symptom association probability; SGB, supragastric belching; SI; symptom index.
[a]$P < .05$ compared with pure reflux hypersensitivity.
[b]$P < .05$ compared with supragastric belching.

Table 2. High-Resolution Manometry and Impedance-pH Monitoring Results in the 3 RH Groups

	Pure reflux hypersensitivity (RH-pure) (N = 59)	Supragastric belching (RH-SGB) (N = 46)	Rumination (RH-RUM) (N = 11)	*P* value
High-resolution manometry				
EGJ morphology type I/II/III	50/7/2	28/16/2 [a]	11/0/0	.010
EGJ-CI (*mm Hg-cm*)	22.3 (13.3–43.3)	29.2 (17.7–40.3)	24.8 (20.9–48.9)	.532
Normal motility/ineffective esophageal motility (n)	42/17	32/14	8/3	1
Impedance-pH monitoring				
Total AET (%)	2.1 (1.1–2.7)	1.9 (0.9–2.9)	1.5 (0.9–2.1)	.415
Upright AET (%)	3.2 (1.5–3.8)	3.2 (1.3–4.3)	2.1 (1.6–3.4)	.655
Recumbent AET (%)	0.0 (0.0–0.4)	0.1 (0.0–0.4)	0.0 (0.0–0.3)	.383
Total reflux episodes (n)	50 (34–63)	52 (37–66)	63 (50–83)	.130
Acid reflux episodes (n)	28 (19–42)	29 (19–40)	34 (22–41)	.831
Non-acid reflux episodes (n)	15 (10–25)	17 (12–31)	29 (20–44) [a]	.023
MNBI 5 cm above LES (*ohms*)	2524 (2175–3303)	2375 (1739–3289)	3631 (2821–3980)	.031
MNBI 3 cm above LES (*ohms*)	2597 (2046–3196)	2562 (1792–3188)	3544 (2952–3932) [a,b]	.031
Total number of SGB	1 (0–5)	38 (25–80) [a]	17 (2–26) [a,b]	<.001

AET, acid exposure time; EGJ, esophagogastric junction; EGJ-CI, EGJ-contractile integral; LES, lower esophageal sphincter; MNBI, mean nocturnal baseline impedance; SGB, supragastric belching.
[a]$P < .05$ compared with pure reflux hypersensitivity.
[b]$P < .05$ compared with supragastric belching.

pure and RH-SGB, whereas patients with RH-RUM had predominant regurgitation (Table 1).

Esophageal Physiology Patterns Within Reflux Hypersensitivity Phenotypes

Esophageal body motility was similar among RH phenotypes; ineffective esophageal motility proportions were also similar (Table 2). The RH-SGB group had type II EGJ morphology more often than RH-pure and RH-RUM groups. In contrast, EGJ pressures (ie, EGJ-contractile integral) were similar across phenotypes.

Patients with RH-RUM had significantly more non-acid reflux than RH-pure and RH-SGB patients. MNBI measurements were normal (>2000 ohms) in the distal channels 3 and 5 cm above the LES in all phenotypes. The RH-RUM group had significantly higher MNBI compared with the other 2 phenotypes.

Relationship Between Supragastric Belching and Gastroesophageal Reflux Disease Symptoms in Patients With Reflux Hypersensitivity With Excessive Supragastric Belching During Impedance-pH Monitoring

Patients with RH-SGB had reflux symptoms (ie, heartburn, chest pain, or regurgitation) rather than belching as their main symptom (Table 3). Overall, they reported 312 episodes of heartburn, 462 episodes of regurgitation, and 26 episodes of chest pain.

SGBs were associated with 40.6% of GERD symptoms (25.0%–66.7%) (Figure 1*D*). SGB causing reflux (18.9% [4.4%–33.3%]) associated with symptoms significantly more often compared with SGB without reflux (7.0% [0.0%–20.0%]; $P = .022$) and SGB during reflux (8.0% [0.0%–22.0%]; $P = .058$) ($P = .014$) (Figure 1*D*).

Relationship Between Possible Rumination Events and Gastroesophageal Reflux Disease Symptoms in Patients With Reflux Hypersensitivity With Rumination During Impedance-pH Monitoring

Patients with RH-RUM had a median of 9 (6–17) possible postprandial rumination episodes on impedance-pH monitoring. In these patients, 40.0% (7.8%–54.5%) of the symptomatic (mainly regurgitation) liquid retrograde events were considered as possible rumination episodes.

Predictive Factors for Presence of Supragastric Belching or Rumination in Patients With Reflux Hypersensitivity

Multivariate analysis showed that abnormal EGJ morphology (type II or III EGJ) was an independent predictive factor for SGB (RH-SGB) (OR, 5.56; 95% CI, 1.64–18.9; $P = .006$) (Supplementary Table 2). On the other hand, younger age (OR, 0.83; 95% CI, 0.71–0.98; $P = .025$) and larger number of non-acid reflux episodes (OR, 1.08; 95% CI, 1.02–1.15; $P = .007$) were associated with RH-RUM (Supplementary Table 3).

Table 3. Characteristics of SGB in the 46 Patients With RH-SGB

	N = 46
Total number of SGBs (n)	38 (25–80)
SGB-induced reflux (n)	13 (8–21)
Acid reflux (n)	8 (4–15)
Non-acid reflux (n)	4 (3–7)
Symptomatic reflux (n)	3 (1–5)
SGBs during reflux (n)	12 (4–21)
Association between SGB and reflux	
Proportion of SGB-induced reflux to the total number of refluxes (%)	29.1 (13.5–55.2)
Proportion of reflux related SGB (-induced or during reflux) to the total number of SGBs (%)	63.6 (39.8–73.5)
Association between SGB and symptoms	
Proportion of SGB-induced symptomatic refluxes to the total number of symptomatic refluxes (%)	34.2 (18.5–51.2)

RH, reflux hypersensitivity; SGB, supragastric belching.

Discussion

On the basis of recent emphasis on behavioral disorders in PPI-refractory states,[14] we hypothesized that undiagnosed behavioral disorders might account for some of the 40% reported refractoriness to RH management.[7–9] We found that 21% of patients with PPI-refractory reflux symptoms investigated with endoscopy/reflux monitoring are initially diagnosed as having RH, and 49% of these patients have pathologic SGB or rumination. Furthermore, in RH-SGB patients, SGB triggered 34% of symptomatic refluxes and explained 41% of GERD symptoms. In RH-RUM patients, 40% of reflux symptoms were associated with possible rumination events.

As many as 24%–34% of symptomatic PPI-refractory patients are reported to have RH.[7–9,11] Our study demonstrated a slightly lower RH prevalence (21%), probably from our stringent definitions requiring strict AET thresholds and both SI and SAP to be positive for RSA, to reduce the likelihood of erroneous categorizing of phenotype.[19,20,27]

Although belching is a common GERD symptom,[31] pathologic numbers of SGBs are identified when excessive belching is a dominant symptom. Alternatively, approximately 40% of patients with pathologic SGB report reflux symptoms rather than belching[16,29]; Hemmink et al[32] also reported that 38% of their SGB patients (9/24) did not have belching as their main symptom. Our prevalence rate of pathologic SGB (34%, 187/543) (Supplementary Table 1) is concordant with other studies showing a similarly high SGB prevalence in GERD patients.

We found a high prevalence of pathologic SGB in both RH and true NERD, and a proportion of SGB may contribute to increased AET in NERD.[16] Alternatively, some patients diagnosed as RH during impedance-pH monitoring could in fact have NERD misdiagnosed because of day-to-day AET variability and may be identified as NERD on prolonged wireless reflux monitoring.[33]

Of 116 patients initially diagnosed as RH, 9.5% had rumination on HRM/Z, a higher proportion than that observed in the NERD and FH groups. A higher prevalence (20%) was reported by Yadlapati et al[14] on postprandial HRM/impedance in PPI-refractory patients, likely related to different study populations. We identified 3 different RH phenotypes, RH-pure, RH-SGB, and RH-RUM, without many physiological differences between phenotypes. Patients with RH-SGB had hiatal hernias more often, whereas patients with RH-RUM had more non-acid reflux and higher MNBI, albeit within the normal range.

Central/peripheral sensitization, psychological comorbidities, and stress can contribute to RH pathophysiology.[34–36] Hidden excessive SGB caused one-third of symptomatic refluxes and underlined 40% of marked reflux symptoms during impedance-pH monitoring in patients with initial RH diagnosis. This finding suggests that in RH-SGB, true hypersensitivity might be accountable for only part of the mechanisms underlying symptoms and explains the poor response to pain modulators. Antidepressants recommended for RH management are not particularly effective for SGB or rumination,[17,18] and patients with RH-SGB typically require a combination of pain modulators and cognitive behavioral therapy.[4,16]

Our findings have both diagnostic and therapeutic implications for patients with PPI-refractory GERD symptoms. Although PPI-refractory patients should be carefully questioned for belching and regurgitation to diagnose hidden behavioral disorders, clinical history alone might not be enough to establish diagnosis of pathologic SGB or rumination. Young patients with predominant postprandial regurgitation will benefit from HRM/Z using a test meal to diagnose rumination or SGB.[37] Although expert interpretation of impedance-pH monitoring is often required, certain tips can lead less experienced readers to identify SGB, rumination, and the different RH phenotypes. In RH patients, more than 60% of SGB are related to reflux events; therefore, initial automatic detection followed by careful manual review of all reflux episodes can identify pathologic SGB. Frequent symptomatic non-acid reflux in the early postprandial period is a characteristic of rumination episodes.[15] On the basis of our current findings, EGJ types II and III, young age, and significant numbers of non-acid reflux episodes should prompt a careful analysis of the impedance-pH tracings for evidence of RH-SGB or RH-RUM. There are potential treatment implications for each RH phenotype. In pure RH, acid suppression and pain modulators are optimized,[7,10] but escalation of PPI dosing or antireflux surgery should only

be considered if a very clear association is demonstrated between acid reflux and symptoms. In RH with SGB, a dual approach using pain modulators and cognitive behavioral therapy could theoretically suffice. In RH with rumination, behavioral intervention with diaphragmatic breathing is considered the best current treatment.[18]

This study has some limitations. First, this is a retrospective single tertiary center study. However, the retrospective analysis helped us to identify phenotypes within a large RH cohort. It is unlikely that a prospectively collected RH cohort would provide different information, because phenotypes were identified on objective impedance pH tracing analysis. Second, it is possible that some ruminators potentially remain undiagnosed, because HRM/Z was used on the basis of the treating clinicians' expectation. Finally, lack of an intervention protocol limits assessment of the clinical utility of phenotyping RH patients. In the second step of our project, a prospective outcome study will define the value of identification of the RH phenotypes in predicting treatment outcomes using cognitive behavioral therapy or pain modulators.

In conclusion, high proportions of RH patients with PPI-refractory esophageal symptoms have hidden SGB or rumination, accounting for up to 41% of symptomatic reflux. These disorders might partly explain the 40% refractoriness to PPI and pain modulators in these patients. Diagnosing SGB or rumination in patients with RH can therefore modify the therapeutic strategy. Prospective outcome studies combining psychological therapies and pain modulators are needed to prove this hypothesis.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2020.03.063.

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Supplementary Table 1. Clinical Characteristics and Findings of Impedance-pH Monitoring in the 3 Groups

	RH (N = 116)	FH (N = 126)	NERD (N = 300)	*P* value
Age (*y*)	39 (31–52)	45 (33–54)	52 (41–60)[a,b]	<.001
Female (n, %)	81 (69.8)	79 (62.7)	168 (56.0)[a]	.030
BMI (kg/m^2)	26.2 (23.0–29.5)	24.9 (22.0–28.0)	27.6 (24.3–31.5)[a,b]	<.001
RDQ	11 (9–12)	10 (8–12)[a]	11 (8–12)[b]	.021
No. of patients having each symptom with positive SI and SAP				
Heartburn (n, %)	33 (28.4)		89 (29.7)	.904
Regurgitation (n, %)	56 (48.3)		53 (17.7)	<.001
Chest pain (n, %)	2 (1.7)		3 (1.0)	.621
Heartburn and regurgitation (n, %)	23 (19.8)		66 (22.0)	.690
Regurgitation and chest pain (n, %)	1 (0.9)		3 (1.0)	1
All 3 symptoms (n, %)	1 (0.9)		4 (1.3)	1
Hiatus hernia >1 cm (n, %)	24 (20.9)	23 (18.5)	116 (40.0)[a,b]	<.001
Impedance-pH monitoring				
Total AET (%)	2.0 (1.0–2.6)	0.5 (0.2–1.5)[a]	11.3 (8.2–17.0)[a,b]	<.001
Upright AET (%)	3.1 (1.4–3.9)	0.8 (0.2–1.8)[a]	12.0 (8.0–17.7)[a,b]	<.001
Recumbent AET (%)	0.1 (0.0–0.4)	0.0 (0.0–0.3)[a]	10.3 (3.4–20.3)[a,b]	<.001
Total reflux episodes (n)	51 (35–66)	19 (12–34)[a]	64 (43–97)[a,b]	<.001
Acid reflux episodes (n)	28 (19–40)	8 (3–16)[a]	46 (30–66)[a,b]	<.001
Non-acid reflux episodes (n)	17 (12–29)	10 (5–17)[a]	12 (6–26)[a]	<.001
SGB >13/24 hours (n, %)	46 (39.7)	28 (22.0)[a]	113 (37.7)[b]	.003
Rumination (n, %)	11 (9.5)	0 (0.0)[a]	4 (1.3)[a]	<.001

AET, acid exposure time; BMI, body mass index; FH, functional heartburn; NERD, non-erosive reflux disease; RDQ, Reflux Disease Questionnaire; RH, reflux hypersensitivity; SAP, symptom association probability; SGB, supragastric belching; SI, symptom index.
[a]$P < .05$ compared with RH.
[b]$P < .05$ compared with FH.

Supplementary Table 2. Univariate and Multivariate Analysis of Predictive Factors of RH-SGB in RH Group

	Crude OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Age	1.01 (0.98–1.03)	.565		
Female	0.36 (0.16–0.80)	.013	0.43 (0.14–1.31)	.137
BMI	0.92 (0.84–1.02)	.102	0.92 (0.82–1.04)	.189
RDQ	0.98 (0.86–1.11)	.728		
Each symptom with positive SI and SAP				
Heartburn	2.36 (1.04–5.37)	.041	2.28 (0.77–6.80)	.139
Regurgitation	0.73 (0.34–1.53)	.402		
Chest pain	1.53 (0.09–25.1)	.765		
Heartburn and regurgitation	0.61 (0.23–1.61)	.316		
Regurgitation and chest pain	0 (0-Inf)	.992		
All 3 symptoms	0 (0-Inf)	.992		
High-resolution manometry				
EGJ morphology II/III	4.36 (1.74–10.9)	.002	6.11 (1.82–20.5)	.003
EGJ morphology III	1.55 (0.21–11.4)	.669		
EGJ-CI	1.00 (0.99–1.02)	.753		
IEM	1.09 (0.48–2.47)	.829		
Impedance-pH monitoring				
Total AET	0.97 (0.69–1.37)	.86		
Upright AET	1.01 (0.81–1.25)	.925		
Recumbent AET	0.93 (0.62–1.41)	.743		
Total reflux episodes	1.00 (0.98–1.01)	.776		
Acid reflux episodes	1.00 (0.98–1.02)	.775		
Non-acid reflux episodes	1.00 (0.98–1.02)	.877		
MNBI 5 cm above LES[a]	0.97 (0.93–1.01)	.169		
MNBI 3 cm above LES[a]	0.98 (0.94–1.02)	.264		

AET, acid exposure time; BMI, body mass index; CI, confidence interval; EGJ, esophagogastric junction; EGJ-CI, EGJ-contractile integral; IEM, ineffective esophageal motility; LES, lower esophageal sphincter; MNBI, mean nocturnal baseline impedance; OR, odds ratio; RDQ, Reflux Disease Questionnaire; RH, reflux hypersensitivity; SAP, symptom association probability; SGB, supragastric belching; SI, symptom index.
[a]OR given for a 100-ohm increase in variable.

Supplementary Table 3. Univariate and Multivariate Analysis of Predictive Factors of RH-RUM in RH Group

	Crude OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Age	0.91 (0.85–0.97)	.004	0.83 (0.71–0.98)	.025
Female	2.06 (0.42–10.1)	.371		
BMI	0.86 (0.71–1.05)	.132	0.83 (0.60–1.16)	.277
RDQ	0.86 (0.71–1.10)	.268		
Symptom with positive SI and SAP				
Heartburn	—	>.99		
Regurgitation	3.17 (0.80–12.6)	.102	2.00 (0.16–24.7)	.59
Chest pain	—	>.99		
Heartburn and regurgitation	1.59 (0.39–6.55)	.518		
Regurgitation and chest pain	—	>.99		
All 3 symptoms	—	>.99		
High-resolution manometry				
EGJ morphology II/III	—	>.99		
EGJ-CI	1 (0.98–1.03)	.844		
IEM	0.90 (0.22–3.6)	.876		
Impedance-pH monitoring				
Total AET	0.70 (0.38–1.28)	.245		
Upright AET	0.83 (0.57–1.21)	.339		
Recumbent AET	0.92 (0.43–1.97)	.838		
Total reflux episodes	1.03 (1.01–1.05)	.013	0.99 (0.92–1.07)	.778
Acid reflux episodes	1.01 (0.98–1.05)	.38		
Non-acid reflux episodes	1.05 (1.01–1.08)	.005	1.08 (1.02–1.15)	.007
MNBI 5 cm above LES[a]	1.08 (1.01–1.16)	.0184		
MNBI 3 cm above LES[a]	1.08 (1.02–1.15)	.0118	1.07 (0.95–1.21)	.267

AET, acid exposure time; BMI, body mass index; CI, confidence interval; EGJ, esophagogastric junction; EGJ-CI, EGJ-contractile integral; IEM, ineffective esophageal motility; LES, lower esophageal sphincter; MNBI, mean nocturnal baseline impedance; OR, odds ratio; RDQ, Reflux Disease Questionnaire; RH, reflux hypersensitivity; RUM, rumination; SAP, symptom association probability; SI, symptom index.

[a]OR given for a 100-ohm increase in variable.