Assessment of the Multiple Rapid Swallows Test for Gauging Esophageal Reflux Burden in Patients with Refractory Gastroesophageal Reflux Disease

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Background:
The multiple rapid swallows (MRS) test is used to assess esophageal contraction reserve. In this study, we characterized the expression of the MRS test in patients with reflux burden and other symptomatic phenotypes with refractory gastroesophageal reflux disease (rGERD).

Material/Methods:
Patients with rGERD who underwent high-resolution manometry (HRM) and esophageal pH-impedance monitoring (EIM) between September 2018 and January 2020 were retrospectively studied.

Results:
We enrolled 151 patients and divided them into 4 phenotypes according to the results of EIM. In phenotype 1, the MRS distal contractile integral (DCI) was significantly positively correlated with acid-liquid reflux episodes. In phenotype 2, lower esophageal sphincter pressure (LES) length was significantly positively correlated with MRS DCI, and MRS/single-swallow (SS) DCI ratio. In phenotype 3, MRS DCI was negatively correlated with the DeMeester score, acid exposure time (AET), upright AET, long-term acid reflux episodes, acid-mixed reflux episodes, recumbent acid reflux episodes, and total acid reflux episodes. There was a significant negative correlation between MRS/SS DCI and recumbent acid reflux episodes. In phenotype 4, nonacid-liquid episodes and recumbent nonacid reflux episodes were significantly higher in the abnormal MRS group. However, acid-gas episodes, weakly acid-gas episodes, and upright gas reflux episodes were higher in the normal MRS group than in the abnormal MRS group.

Conclusions:
Esophageal contraction reserve is heterogeneous within the reflux burden and symptomatic phenotypes of patients with rGERD.

Keywords:
Esophageal Motility Disorders • Esophageal pH Monitoring • Gastroesophageal Reflux • Gastrointestinal Diseases

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Background

Refractory gastroesophageal reflux disease (rGERD) is considered as a heterogeneous group of symptoms, which are typically treated with various proton pump inhibitor (PPI) dosing regimens; responses of patients to therapy vary widely [1]. The common potential causes of rGERD are esophageal motility disorder, delayed gastric emptying, functional diseases of the upper digestive tract, weakly acidic or nonacidic reflux, insufficient acid suppression, and esophageal hypersensitivity [2].

The importance of esophageal motility cannot be ignored in the study of the pathogenesis of rGERD. The modern-day criterion standard for esophageal motor assessment is esophageal high-resolution manometry (HRM) [3]. However, esophageal contraction reserve has been proposed as a new method. Currently, the multiple rapid swallows (MRS) test is commonly used to estimate esophageal contraction reserve [4] and assess inhibitory swallowing mechanisms [5].

Ambulatory reflux monitoring can provide confirmatory evidence of rGERD, and using esophageal pH-impedance monitoring (EIM), 4 phenotypes of patients with rGERD can be identified: symptomatic GERD (sGERD), hypersensitive esophagus (HE), GERD but with symptoms not directly related to it (nsGERD), and functional disorder. Each has unique management considerations [6]. To date, few studies have assessed the correlation between rGERD and esophageal contraction reserve. This retrospective study evaluated esophageal contraction reserve using the HRM and the MRS test and characterized the results by phenotype.

Material and Methods

Subjects

Patients with rGERD who underwent HRM and 24 h EIM were selected retrospectively between September 2018 and January 2020. Inclusion criteria were as follows: age ≥18 years old, score ≥8 on the gastroesophageal reflux symptoms questionnaire [7] and poor efficacy of PPI treatment for 8 weeks, having undergone a gastroscopy examination and evaluation of esophagitis [8]. The severity of esophagitis was graded from A to D by the Los Angeles (LA) classification system. Patients with esophageal tumor, disorders with esophagogastric junction (EGJ) outflow obstruction, major disorders of esophageal motility, or previous gastroesophageal surgery were excluded. All patients underwent HRM and 24 h EIM; drugs influencing esophageal motor function or gastric acid secretion were weaned off at least 1 week before these tests. The study was approved by the Ethics Committee of Beijing Tongren Hospital, Capital Medical University (TRECKY2019-114).

GERD-Q Score

Patients defined the severity of symptoms using the GERD-Q questionnaire (**Table 1**) [7]. Four positive symptoms of GERD (heartburn and regurgitation), sleep disturbance because of reflux, use of medication in addition; 2 negative predictors of GERD (abdominal pain and nausea) were included. For positive symptoms, scores ranged from 0 to 3, and from 3 to 0 for negative symptoms. The total GERD-Q score ranged of 0-18. A GERD-Q score ≥8 was considered to indicate positivity. GERD-Q score adopted authoritative Chinese translation version. In addition, when participants filled in the questionnaire, researchers would explain each item in detail to the participants. That could increase the accuracy of GERD-Q score, rather than filling in the questionnaire by patients alone, so as to eliminate the differences in understanding and language.

HRM

HRM was performed with Solar GI HRM (MMS, Enschede, The Netherlands). The operation process and diagnosis of HRM includes the recommended standardized protocol on the basis of Chicago Classification (CC) version 3.0 [9]: a baseline recording of esophageal sphincter pressure, and then patients are asked to swallow 5 ml water 10 times to assess esophageal motility. With MRS, patients took five 2-ml swallows <4 s apart (**Figure 1**). Then, the following parameters are recorded: lower esophageal sphincter pressure (LESP), single-swallow (SS) distal contractile integral (DCI), MRS DCI, distal latency (DL), contractile front velocity (CFV), and the 4-s integrated relaxation pressure (IRP4s). Analyses of contraction reserve require the calculation of mean SS DCI plus MRS DCI. Abnormal MRS contraction was defined as MRS/SS DCI <1. The presence of contraction reserve using the MRS/SS DCI ratio was considered the criterion standard for the purpose of this study. The patients were classified into 2 groups according to MRS results: normal MRS (ratio between DCI following MRS to the mean DCI after SS ≥1) and abnormal MRS (ratio between DCI following MRS to the mean DCI after SS <1).

EIM

EIM for 24 h was used to record the frequency and property of gastroesophageal reflux. After calibration in buffer solutions, a pH-impedance catheter was inserted into the esophagus 5 cm above the lower esophageal sphincter pressure (LES), with the pH sensor at 5 cm and the impedance channels at 3, 5, 7, 9, 15, and 17 cm. Meals, postures, and symptoms were recorded by patients. The EIM data were analyzed by 2 investigators (JC and BG). Reflux episodes were characterized as acid (pH ≤4), weakly acid (4< pH <7), or nonacid (pH ≥7), and liquid, mixed, or gas based on the value of impedance. The normal values and analysis were according to the study of Zerbib et al [10].

Table 1. GERD-Q questionnaire [7].

| Question (symptoms over the previous week)	Frequency score			
	0 day	1 day	2-3 days	4-7 days
1. How often did you have a burning feeling behind your breastbone (heartburn)?	0	1	2	3
2. How often did you have stomach contents (liquid or food) moving upwards to your throat or mouth (regurgitation)?	0	1	2	3
3. How often did you have a pain in the center of the upper stomach?	3	2	1	0
4. How often did you have nausea?	3	2	1	0
5. How often did you have difficulty getting a good night's sleep because of your heartburn and　or regurgitation?	0	1	2	3
6. How often did you take additional medication for your heartburn and　or regurgitation, other than what the physician told you to take?	0	1	2	3
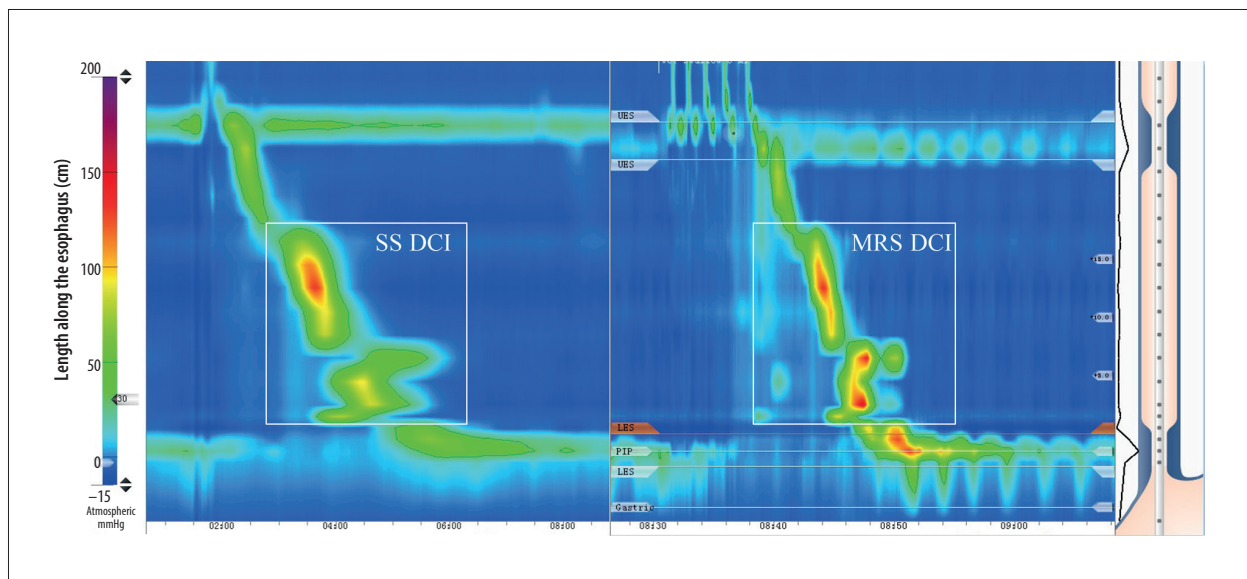
Figure 1. The MRS consists of swallowing 2 mL of water in 4-6 swallows separated by less than or equal to 4 s. MRS DCI >SS DCI was defined normal MRS. DCI – distal contractile; SS – single swallow; MRS – multiple rapid swallow.

The EIM analyzed included the DeMeester score, acid exposure percent time (AET), mean acid clearance, bolus exposure percent time (BET), bolus clearance time (BCT), total reflux events, proximal reflux events, and the characters and numbers of reflux episodes. The symptom index (SI), defined as the ratio of the number of symptoms when reflux episodes occurred to the total number of symptoms recorded [11], was chosen to learn symptom correlations with reflux. Mean nocturnal baseline impedance (MNBI) was assessed from the most distal impedance channel during the night-time period. Three 10-min time periods were selected and the mean was calculated to obtain the MNBI; time periods including swallows, refluxes, and pH drops were excluded [12].

Using EIM, 4 phenotypes of poorly responsive patients were identified, as given in the Introduction (**Figure 2**).

Statistical Analyses

Statistical comparisons were performed using SPSS ver. 22. Normally distributed continuous data are expressed as mean±SD and were compared using the *t* test or one-way ANOVA. Skewed data are shown as medians with interquartile ranges (IQRs). Continuous variables were compared nonparametrically using the Kruskal-Wallis test or Mann-Whitney U test, as appropriate. Categorical data were analyzed using the Pearson χ^2 test. The correlations between MRS/SS DCI ratio and other parameters were analyzed by Pearson's correlation coefficient analyses. The mean difference was significant at the 0.05 level.
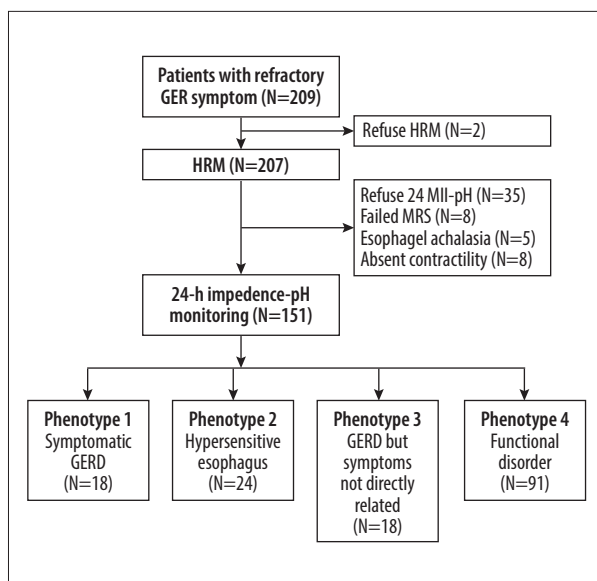
Figure 2. Subject flow.

Results

Clinical Manifestations

We enrolled 151 participants (72 men and 79 women, mean age of 54.53±13.35 years). All patients had GERD-Q scores ranging from 8 to 15. The median GERD-Q score was 8 (IQR 8, 11). Eighty-one patients were diagnosed with erosive esophagitis by gastroscopy, including 5 patients with LA-C or -D esophagitis, and 37 participants had an esophageal hiatus hernia. Body mass index (BMI) (p=0.018) and rate of esophageal hiatus hernia (p=0.025) differed significantly among phenotypes. There were no significant differences in any other parameters. Demographic and clinical characteristics of patients are shown in **Table 2**.

Esophageal Contraction Reserve in Different Phenotypes

No patients had fragmented peristalsis. HRM identified 71 (47.02%) with ineffective esophageal motility (IEM) and 80 (52.98%) with normal esophageal motility.

There were 18 patients with phenotype 1. The median MRS DCI value was 209.50 mmHg·s·cm (IQR 65.50, 507.00) in the abnormal MRS group and 807.00 mmHg·s·cm (440.00, 1755.75) in the normal MRS group (p=0.016). There were no differences in parameters other than MRS DCI (p>0.05).

There were 24 patients with phenotype 2 (HE). The median MRS DCI was 370.50 mmHg·s·cm (40.25, 526.50) in the abnormal group and 650 mmHg·s·cm (414.25, 1045.75) in the normal group (p=0.014). The normal MRS group had a longer LES (3.16±0.52 cm vs 2.77±0.33 cm, p=0.035).

In phenotype 3 (18 participants), the normal group had a higher median MRS DCI (866.00 mmHg·s·cm [496.50, 1206.00]) than the abnormal group (224.00 mmHg·s·cm, [35.00, 463.00]) (p=0.002). However, other parameters did not differ between the 2 groups.

Table 3 summarizes the parameters of HRM and 24 h EIM for phenotype 4. Again, the median MRS DCI of the normal MRS group was higher than the abnormal MRS group (730.00 mmHg·s·cm vs 239.50 mmHg·s·cm, p<0.05). There were no differences in the SS DCI, CFV, esophageal peristalsis break, DL, IRP4s, MRS IRP4s, length of LES, or LESP between the 2 groups (all p>0.05).

As detailed in the table, of the 91 patients with phenotype 4, there were significantly more acid-gas episodes, weakly acid-gas episodes, and upright gas reflux episodes in the normal group, but more nonacid-liquid episodes and recumbent nonacid reflux episodes in the abnormal MRS group. There were no differences in any other parameters.

Correlation Between Esophageal Contraction Reserve and Esophageal Motility/Reflux Episodes

Figure 3 illustrates the correlation between esophageal contraction reserve and motility or reflux burden using correlation heatmaps. In phenotype 1 (sGERD), SS DCI was positively correlated with LESP (r=0.485, p=0.041) and break (r=-0.624, p=0.006). Similarly, correlations were found between MRS DCI and acid-liquid reflux episodes (r=0.499, p=0.035). There was a significant negative correlation between MRS/SS DCI ratio and LES length (r=-0.495, p=0.041).

In phenotype 2 (HE), there were negative correlations between SS DCI and CFV (r=-0.498, p=0.013) and break (r=-0.584, p=0.003). Length of LES was significantly positively correlated with MRS DCI (r=0.584, p=0.003) and MRS/SS DCI (r=0.406, p=0.049).

In phenotype 3 (nsGERD), MRS DCI was negatively correlated with DeMeester score (r=-0.558, p=0.016), AET (r=-0.573, p=0.013), upright AET (r=0.482, p=0.043), long-term acid reflux episodes (r=-0.575, p=0.013), acid-mixed reflux episodes (r=-0.486, p=0.041), acid reflux episodes (recumbent) (r=-0.534, p=0.022), and total acid reflux episodes (r=-0.470, p=0.049). There was a significant negative correlation between MRS/SS DCI and acid reflux episodes (recumbent) (r=-0.526, p=0.025).

In phenotype 4, good correlations were only found between break and SS DCI (r=-0.643, p=0.000) and MRS DCI (r=-0.441, p=0.000). SS DCI was positively correlated with IRP4s (r=0.218), CFV (r=0.242), and LESP (r=0.369). MRS DCI was positively correlated with CFV (r=0.228), LESP (r=0.303), long-term acid reflux episodes (r=0.221), weakly acid-gas reflux episodes (r=0.277),

Table 2. Characteristics of the participants (N=151).

	Phenotype 1 n=18	Phenotype 2 n=24	Phenotype 3 n=18	Phenotype 4 n=91	p Value
Age (years)	57.28±16.24	52.42±14.41	58.17±12.31	53.84±12.63	0.403
Gender (M/F)	9/9	10/14	10/8	43/48	0.840
Height (m)	1.64±0.11	1.65±0.08	1.64±0.09	1.65±0.09	0.959
Weight (kg)	68.67±11.97	66.23±11.35	67.47±10.27	62.93±9.99	0.079
BMI (kg/m²)	25.42±2.75	24.19±3.83	24.98±3.61	23.14±3.24	0.018*
GERD-Q score	9.5 (8, 12)	8.5 (8, 11)	10 (8, 11)	8 (8, 10)	0.165
Endoscopic finding					
Erosive esophagitis	77.78%	50.00%	55.56%	49.45%	0.171
Esophageal hiatal hernia	38.89%	16.67%	50.00%	20.88%	0.025*
HRM					
CC (IEM/N)	11/7	14/10	5/13	41/50	
SS DCI (mmHg·s·cm)	389.50 (130.25, 774.75)	405.00 (181.50, 893.75)	504.00 (353.50, 1029.75)	510.00 (274.00, 948.00)	0.494
MRS DCI (mmHg·s·cm)	405.00 (101.50, 855.00)	472.50 (206.50, 876.00)	495.50 (184.75, 925.75)	422.00 (159.00, 849.00)	0.986
MRS/SS DCI (mmHg·s·cm)	0.98 (0.61, 1.52)	0.97 (0.54, 1.70)	0.93 (0.29, 1.32)	0.87 (0.50, 1.23)	0.615
CFV (cm/s)	4.00 (3.28, 5.08)	4.65 (3.98, 5.48)	4.35 (3.63, 5.80)	4.60 (3.70, 5.50)	0.326
Break (cm)	2.50 (0.65, 3.90)	2.30 (1.30, 4.53)	1.70 (1.00, 4.00)	2.10 (1.10, 3.80)	0.867
DL (s)	6.65 (6.08, 7.53)	7.25 (6.23, 7.85)	6.80 (6.20, 7.30)	6.80 (6.10, 7.40)	0.720
IRP4 (mmHg)	2.00 (-2.25, 2.00)	1.00 (0, 4.00)	-0.50 (-2.00, 2.00)	1.00 (-1.00, 4.00)	0.103
MRS IRP4 (mmHg)	0 (-1.25, 2.25)	1.00 (-2.00, 4.25)	0 (-1.00, 2.00)	1.00 (-1.00, 4.00)	0.557
LESP (mmHg)	5.00 (3.75, 8.50)	7.50 (2.00, 14.00)	5.50 (2.75, 9.50)	5.00 (1.00, 10.00)	0.660
Length of LES (cm)	2.82±0.51	2.97±0.47	2.93±0.52	2.91±0.42	0.749

Data are shown as the mean±SD, median (IQR) or number (%) of patients. BMI – body mass index; GERD – gastroesophageal reflux disease; CC – Chicago Classification; IEM – ineffective esophageal motility; N – normal; SS – single swallow; MRS – multiple rapid swallows; DL – distal latency; DCI – distal contractile integral; CFV – contractile front velocity; IRP – integrated relaxation pressure; LESP – lower esophageal sphincter pressure.

upright gas reflux episodes (r=0.212), and MNBI (r=0.304). MRS/SS DCI was positively correlated with acid-gas reflux episodes (r=0.301), weakly acid-gas reflux episodes (r=0.292), upright gas reflux episodes (r=0.281), total gas reflux episodes (r=0.244), and MNBI (r=0.305), but all of the positive correlation coefficients were <0.4 (p<0.05). However, SS DCI was negatively correlated with DL (r=-0.272), DeMeester score (r=-0.260), AET (r=-0.219), long-term acid reflux episodes (r=-0.292), and upright nonacid reflux episodes (r=-0.230). MRS DCI was negatively correlated with DL (r=-0.248), nonacid-liquid reflux episodes (r=-0.255), and recumbent nonacid reflux (r=-0.275). MRS/SS DCI was negatively correlated with nonacid-liquid reflux episodes (r=-0.267), and recumbent nonacid reflux (r=-0.364). Similarly, all of these correlations were poor (p<0.05).

Table 3. High-resolution manometry and 24-h impedance-pH monitoring parameters of Phenotype 4.

	Normal MRS		Abnormal MRS		p Value
CC ver3.0 (n)					
IEM	17		24		
Fragmental peristalsis	0		0		
Normal esophageal motility	22		28		
EGJ morphology (type I/II/III)	22/11/6		30/16/6		
HRM Parameters Mean±SD/Median (IQR)					
SS DCI (mmHg·s·cm)	507.00	(259.00, 921.00)	541.00	(309.25, 992.50)	0.566
MRS DCI (mmHg·s·cm)	730.00	(268.00, 1136.00)	239.50	(69.50, 540.75)	<0.001*
CFV (cm/s)	4.60	(3.70, 5.20)	4.60	(3.72, 5.60)	0.647
Break (cm)	2.40	(1.10, 4.20)	1.90	(1.13, 3.60)	0.665
DL (s)	6.70	(6.20, 7.30)	6.85	(6.00, 7.50)	0.832
IRP4 (mmHg)	1.00	(-1.00, 3.00)	2.00	(0.00, 5.00)	0.106
MRS IRP4 (mmHg)	1.00	(-1.00, 4.00)	1.00	(-1.00, 5.00)	0.803
LESP (mmHg)	5.00	(1.00, 9.00)	5.50	(1.25, 11.75)	0.635
Length of LES (cm)	2.94±0.46		2.88±0.40		0.502
pH-Impedance parameters					
DeMeester score	3.20	(0.77, 6.98)	2.70	(0.55, 7.63)	0.642
AET (%)	0.80	(0.10, 2.00)	0.55	(0.10, 1.78)	0.459
BET (%)	0.50	(0.20, 0.90)	0.50	(0.20, 0.80)	0.990
BCT (s)	7.00	(6.00, 10.00)	6.00	(5.00, 9.00)	0.087
Total reflux events (n)	13.30	(4.00, 18.60)	8.50	(2.10, 18.18)	0.316
Long-term acid reflux episodes (s)	2.90	(1.10, 6.00)	2.50	(0.50, 6.60)	0.907
Proximal extent (n)	6.30	(2.10, 18.60)	6.80	(2.10, 26.55)	0.490
Acid-Liquid episodes (n)	0.00	(0.00, 1.00)	0.00	(0.00, 1.00)	0.855
Acid-Mixed episodes (n)	1.00	(0.00, 2.00)	1.00	(0.00, 2.00)	0.534
Acid-Gas episodes (n)	2.00	(1.00, 6.00)	1.00	(0.00, 2.00)	0.004*
Weakly acid-Liquid episodes (n)	5.00	(1.00, 9.00)	4.00	(2.00, 9.00)	0.901
Weakly acid-Mixed episodes (n)	15.00	(4.00, 32.00)	13.50	(4.25, 28.00)	0.647
Weakly acid-Gas episodes (n)	46.00	(29.00, 70.00)	25.50	(15.25, 46.50)	0.001*
Nonacid-Liquid episodes (n)	1.00	(0.00, 3.00)	3.00	(0.00, 13.25)	0.024*
Nonacid-Mixed episodes (n)	5.00	(1.00, 14.00)	4.00	(1.00, 16.75)	0.872
Nonacid-Gas episodes (n)	26.00	(15.00, 37.00)	20.00	(12.50, 33.75)	0.480
MNBI (ohms)	2596.95±614.17		2485.38±621.66		0.397

Table 3 continued. High-resolution manometry and 24-h impedance-pH monitoring parameters of Phenotype 4.

	Normal MRS		Abnormal MRS		p Value
Impedance parameters upright					
Acid reflux episodes (n)	1.10	(0, 2.20)	1.00	(0, 2.88)	0.960
Weakly acidic reflux episodes (n)	18.20	(7.50, 35.90)	14.85	(4.43, 30.85)	0.218
Nonacid reflux episodes (n)	7.30	(1.20, 15.00)	5.95	(1.03.23.58)	0.936
Liquid reflux episodes (n)	4.40	(2.10, 8.30)	6.75	(2.20, 13.35)	0.212
Mixed reflux episodes (n)	25.40	(7.60, 45.80)	17.50	(8.28, 36.00)	0.303
Gas reflux episodes (n)	69.00	(48.50, 102.50)	45.30	(29.20, 68.18)	0.001*
Recumbent					
Acid reflux episodes (n)	0.00	(0, 1.10)	0.00	(0.00, 0.00)	0.392
Weakly acidic reflux episodes (n)	4.20	(1.10, 10.50)	4.35	(1.33, 12.15)	0.377
Nonacid reflux episodes (n)	0.00	(0, 2.20)	1.65	(0, 7.25)	0.004*
Liquid reflux episodes (n)	2.20	(1.00, 5.50)	2.65	(1.10, 8.38)	0.396
Mixed reflux episodes (n)	2.20	(1.00, 8.30)	3.50	(1.10, 9.78)	0.261
Gas reflux episodes (n)	10.50	(4.10, 15.20)	7.45	(3.13, 17.45)	0.742

Data are shown as the mean±SD or median (IQR). CC – Chicago Classification; IEM – ineffective esophageal motility; N – normal; SS – single swallow; MRS – multiple rapid swallows; CFV – contractile front velocity; DCI – distal contractile integral; DL – distal latency; IRP – integrated relaxation pressure; LESP – lower esophageal sphincter pressure; MNBI – mean nocturnal baseline impedance; AET – acid exposure percent time; BET – bolus exposure percent time; BCT – bolus clearance time.

Discussion

As the rGERD diagnostic paradigm evolves, using supplementary diagnostic testing to define a precise approach tailored to the individual patient becomes possible. An assessment of motor function, reflux burden, and symptomatic phenotype will therefore help disease management. The Lyon Consensus recommends that every HRM exam should be accompanied by a provocative test [13], and the most frequently used tool is the MRS test [14]. Esophageal smooth muscle has the capacity to augment contraction when provoked with repetitive swallowing [15] and this is termed contraction reserve [16]. A novel parameter for the evaluation of contraction reserve was recently introduced: the ratio between the DCI after MRS and the average DCI of 10 SSs (MRS/SS DCI ratio) [5]. When added as an adjunctive diagnostic tool to the SS, the MRS is reproducible [17] and can help detect abnormalities in symptomatic patients that are normal according to the CC.

Several studies have investigated the clinical role of MRS in GERD patients. The most notable clinical benefit is related to aiding the prediction of developing post-fundoplication dysphagia [18]. In patients susceptible to gastroesophageal reflux, a lesser contractile reserve is associated with greater esophageal acid exposure and a greater number of reflux events among patients with non-erosive GERD [19]. Furthermore, clinical application of contraction reserve assessment with MRS could help identify patients that may benefit from escalation of reflux therapies or even potentially those likely to benefit from promotility therapy [20].

In our study, MRS DCI was positively correlated with acid-liquid episodes. This suggests that sGERD patients exhibit a compensatory increase in esophageal motility reserve caused by the acid-liquid reflux burden. Phenotype 2 patients can also be quite challenging to treat as they have physiological evidence of GERD, complicated by esophageal hypersensitivity, which diminishes the efficacy of conventional therapy [6]. We found that MRS did not indicate the burden of reflux in these patients. Even more complex are phenotype 3 patients, who have excessive reflux, but in whom a temporal association between symptoms and reflux episodes is not apparent. Technically, these patients have GERD, but treatment of GERD may or may not improve their persistent symptoms [6]. In our research, the lower the MRS DCI, the heavier the acid burden, particularly in the recumbent position, because there was a paucity of primary peristalsis, lack of salivation, and relative hyposensitivity to esophageal acid exposure.
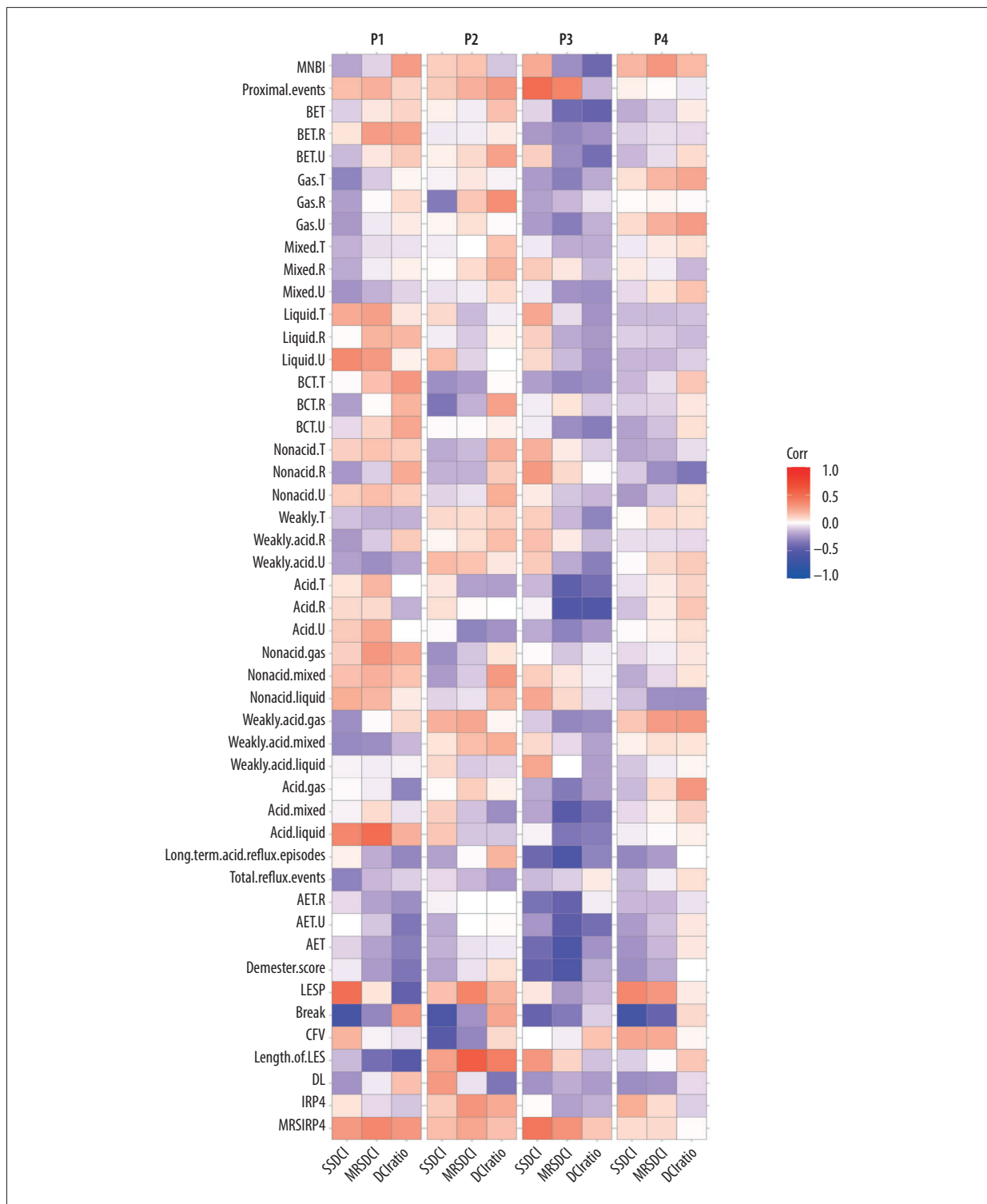
Figure 3. Correlation matrix for the 4 phenotypes of symptomatic reflux. Some parameters were negatively related, represented in blue, and others were positively related, represented in red. The darker the color, the higher the correlation was. P – phenotype; T – total; U – upright; R – recumbent; SS – single swallow; MRS – multiple rapid swallows; DL – distal latency; DCI – distal contractile integral; CFV – contractile front velocity; IRP – integrated relaxation pressure; LESP – lower esophageal sphincter pressure; MNBI – mean nocturnal baseline impedance; AET – acid exposure percent time; BET – bolus exposure percent time; BCT – bolus clearance time.

According to a previous study [6], patients with phenotype 4 are the easiest to manage, as a diagnosis of GERD can be excluded. However, in our clinical practice, the management of these patients remains troublesome. Among the participants included in this study, phenotype 4 accounted for the highest proportion. This indicates that most of the patients diagnosed as having GERD and prescribed PPIs may not have had GERD at all, but rather may have had a functional disorder, defined according to 24-h EIM. In our study sample, nonacid-liquid reflux episodes in the recumbent position were more common in the abnormal MRS group. However, it was puzzling that the normal MRS group had more acid-gas, weakly acid-gas, and upright gas reflux episodes. In light of these data, one might argue that new therapeutic approaches should target decreasing the gas component of the refluxate [21], but the correlations were weak between MRS and the composition of refluxes. These results highlight the complexity of the etiology of functional disorder diseases, emphasizing that esophageal contraction reserve may not be the only factor involved in physiological reflux.

Overall, esophageal acid burden was correlated with esophageal contraction reserve in patients with true GERD (phenotypes 1 and 3). For sGERD (phenotype 1), the regurgitation of acid-liquid required a stronger reserve of esophageal contraction, which could be considered a positive feedback of esophageal peristalsis. For nsGERD, the reserve of esophageal contractile function may occur first, and then lead to prolonged AET and increased acid-mixed reflux episodes. Our data indicate that, for phenotype 1, more aggressive acid suppression treatment was required. In contrast, for phenotype 3, physical properties such as mixed liquid–gas composition, rather than

the chemical composition of reflux episodes, may determine whether reflux episodes are likely to be symptomatic [21]. Symptoms such as heartburn do not appear to be stimulus-specific. Prolonged pH monitoring studies have revealed a poor correlation between acid reflux episodes and heartburn sensation [22]. This suggests the need for new prokinetics drugs as an adjuvant therapeutic strategy, in addition to the traditional therapy with PPIs.

This study had several limitations. It was a retrospective and single-center study, and the results can only be generalized after replication in a larger multicenter study. The inconsistency in normative MRS data may be related to the fact that only 1 MRS maneuver was performed in each patient; recent data suggest that a minimum of 3 maneuvers should be performed for optimal assessment of contraction reserve [16]. The small sample sizes of patients with phenotypes 1, 2, and 3 limit the statistical power of our results. Finally, comparison data from a healthy adult population were not available.

Conclusions

In summary, we compared the MRS results among 4 phenotypes of rGERD using HRM. We found that the relationship between the MRS and reflux burden was heterogeneous within the different phenotypes. As rGERD is a family of syndromes with a complex matrix of pathophysiologies, in the future we will place more attention on the management of rGERD and the understanding of various pathophysiological changes in different phenotypes of rGERD to provide a basis for precise treatment.

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