Assessment of Esophageal Motility Disorders in Patients With Refractory Gastroesophageal Reflux Disease

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Abstract- There is insufficient data about esophageal body dysmotility in patients with refractory gastroesophageal reflux disease (RGERD) and inadequate response to proton pump inhibitors (PPIs) treatment. This study aimed to assess esophageal motility disorder and reflux parameters among these patients by high-resolution manometry (HRM) and intraluminal impedance and pH (MII- pH) monitoring after stopping PPI therapy. A retrospective study was conducted among 100 RGERD patients admitted to Taleghani Hospital (Tehran, Iran) for one year. More than half of them were males (55%). Their mean age was 47.10±6.92, and 50% of patients had ineffective esophageal motility (IEM). Middle, distal, and proximal esophageal pressure (MEP, DEP, and PEP), lower esophageal sphincter (LES) basal pressure (LESP), integrated relaxation pressure (IRP), distal contractile integral (DCI), large breaks, upper esophageal sphincter basal pressure (UESP), and LES length (LESL) in IEM patients were significantly lower than the patients with normal esophageal motility (P<0.001). Furthermore, there were more patients in the IEM group with long-term and abnormal weakly acid reflux compared with the non-IEM group (P<0.05). It seems that the evaluation of reflux parameters and esophageal motility could lead to additional insights into the pathophysiological mechanisms of RGERD. Nevertheless, further studies are suggested to evaluate the effects of esophageal motility disorders among RGERD patients.

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Introduction

Gastroesophageal reflux disease (GERD) is characterized by the reflux of stomach contents and flow back into the esophagus, leading to bothersome symptoms and complications, including chest pain, cough, heartburn, regurgitation, and hoarseness (1). GERD is a prevalent digestive disease (2), and the incidence in the global population has increased in recent years (3). It has negative impacts on patients' quality of life (4). Proton pump inhibitors (PPIs) reduce acid production, and they are in the front line for GERD treatment (5). Nevertheless, a significant percentage of GERD patients might have an inadequate response to PPI therapy (6). Patients are considered to have refractory GERD (RGERD) when they have typical symptoms with poor response to twice-daily dose PPI therapy for at least 12 weeks (7), and they do not achieve adequate symptomatic improvement (8,9).

It has been indicated that GERD is related to upper gastrointestinal dysmotility (UGD), which leads to decreased defense against the refluxate and increased reflux (10). Ineffective esophageal motility (IEM) is a frequent problem among GERD patients, comprising increased intra-abdominal pressure, low peristaltic amplitude, decreased lower esophageal sphincter (LES)

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basal pressure, and prolonged transient LES relaxation (TLESR) (11,12). The role of LES has been widely explored in GERD pathogenesis, while less focus was on esophageal peristalsis and its contribution to esophageal clearance (13).

High-resolution manometry (HRM) is an easily conducted and precise technique compared with conventional manometry for the assessment of individuals with esophageal disorders (14). This method provides a dynamic pressure profile through the whole esophagus (15). In addition, 24-hour multichannel intraluminal impedance-pH (MII-pH) monitoring is an accurate technique to characterize and detect reflux incidences such as pathological and physiological acid, alkaline, and weak acid reflux (16). However, there is a limited number of studies related to patients with RGERD comparing reflux parameters, motility patterns, and the main manometric features (13). The current study investigated the application of HRM and MII-pH monitoring to assess esophageal motility disorders and characterize reflux events among patients with RGERD in patients after stopping PPI therapy.

Materials and Methods

This retrospective study was carried out among 100 RGERD patients referred to the Taleghani Hospital in Tehran, Iran, from April 2020 to April 2021. The Ethics Committee of Shahid Beheshti University of Medical Sciences (SBMU) approved the protocol of this study (IR. SBMU.RIGLD. REC.1395.108). Eligible patients were older than 18 years and had typical regurgitation or heartburn for more than 6 months (17). In addition, they were under treatment with omeprazole 20 mg or rabeprazole 10 mg bid for at least 12 weeks, while their symptoms enhancement was less than 50%, and they were assigned as RGERD patients (18). All of them underwent an endoscopic procedure one month before analysis, and the Los Angeles classification system of GERD (19) was applied to assess the grade of esophageal mucosal injury. Patients were excluded if they had abnormalities other than chronic superficial gastritis or erosive esophagitis, severe esophageal dysmotility, history of gastrointestinal surgery or tumor, and peptic ulcers.

High-resolution manometry

Patients with RGERD, after stopping PPIs, prokinetic or H2-antagonist treatment for at least one week, underwent esophageal MII-pH testing and HRM. The HRM catheter was located transnasally to record activity from the hypopharynx to the stomach. The HRM procedure included a one-minute baseline recording and ten single swallows of 5 mL water. Data were analyzed by the commonly used software (ManoView version 3.0). IEM was considered ≥50% ineffective swallows (DCI≤450 mmHg·sec·cm) using the Chicago Classification Criteria (20). Esophagogastric junction (EGJ) morphology was classified into three subtypes according to the distance between the crural diaphragm (CD) and LES. They were divided into type I (no observable separation between CD and LES), type II (>1 and <2 cm separation), and type III (more than 2 cm separation). The subsequent metrics were recorded: distal contractile integral (DCI), integrated relaxation pressure (IRP), distal esophageal pressure (DEP), middle esophageal pressure (MEP), proximal esophageal pressure (PEP), large breaks, LES basal pressure (LESP), LES length (LESL), and upper esophageal sphincter basal pressure (UESP).

MII-pH monitoring

RGERD patients underwent 24-hour ambulatory MII-pH monitoring. The catheter was inserted via the nostril into the distal esophagus. The pH electrode was situated at 5 cm above the LES, and 6 impedance values (z1-z6) were measured at six sites (3, 5, 7,9,15, and 17 cm upper the LES). In addition, patients were requested to report the occurrence of heartburn or regurgitation symptoms, time of assuming the supine position, and mealtimes. Ambulatory 24-h esophageal pH testing was recorded using a 15 cm antimony catheter and a pH-sensitive microelectrode (Synectics Digitrapper MK III). Results were analyzed and recorded applying Microsoft esophagram. The reflux parameters were documented, which were DeMeester score, frequency of long-term acid reflux of more than five minutes, number and type of reflux episodes, acid exposure time (AET), and percentage of time that esophageal pH was less than 4 in the supine. In addition, AET has considered the total time that the PH in the distal esophagus was less than four, divided by the total time of MII-PH monitoring (21,22). The reflux parameters and events were analyzed by using automated analysis software. Weakly alkaline and acid refluxes, as well as acid reflux episodes, were recorded (23). However, weakly alkaline refluxes are very uncommon; they were combined with weakly acidic refluxes in the analysis and considered nonacid reflux (24). Abnormal acid exposure was assigned for AET above 4.2%. The patients had abnormal reflux when reflux indicators, including frequency of reflux episodes and percentage of reflux time, were more than the normal

limit.

Statistical methods

Data were statistically analyzed by applying SPSS software, version 23. Findings were illustrated as a percentage (%), mean, and standard deviation (SD). In addition, the independent t-test and chi-square test were utilized. The *P* below 0.05 was considered statistically significant.

Results

In this study, a total of 100 RGERD patients were assessed. More than half of them were males (55%). Their mean age was 47.1±6.9. All enrolled patients underwent HRM and MII-pH monitoring with no adverse feedback. Fifty-four patients with erosive esophagitis and 46 non-erosive patients were identified by endoscopy, and they did not have Barrett's esophagus. In addition, 45, 55, and 25 patients had abnormal acid, alkaline, and weak acid reflux based on the findings of MII-pH monitoring. Baseline data are explored in Table 1. None of the patients had major peristalsis disorders and esophagogastric junction outflow obstruction (EGJOO). IEM was observed in 50 % of RGERD patients based on HRM evaluation.

Table 1. Characteristics of patients with RGERD (n=100)

Characteristics		**(Mean±SD)**
Age (years)		47.10±6.92
		n (%)
Male		55 (55)
Female		45 (45)
Upper endoscopy findings	**Erosive esophagitis**	54(54)
	Non-erosive reflux disease	46 (46)
Patients with abnormal reflux	**Acid reflux**	45(45)
	Alkaline reflux	55(55)
	Weakly acid reflux	25(25)

Forty-four large peristaltic breaks were identified between 1000 wet swallows. There were significantly more occurrences of large breaks among patients in the IEM group than those in the non-IEM group with normal esophageal motility (*P*<0.001). LESL, LESP, UESP, PEP, DEP, DCI, MEP, and IRP in the IEM group were significantly lower than the non-IEM group (*P*<0.001) (Table 2). Furthermore, the IEM group had significantly more patients with long-term and abnormal weakly acid reflux in comparison with the non-IEM group (*P*<0.05). Moreover, there were significant mean episodes differences in acid, alkaline, and weakly acid reflux between the two groups (*P*<0.001) (Table 3).

Table 2. HRM measurements between RGERD patients with IEM and normal esophageal motility (n=100)

		IEM (n=50)	**Normal (n=50)**	***P***
		n (%)	**n (%)**	
Male		30 (60)	25(50)	0.315
Female		20 (40)	25(50)	
Large breaks		32(64)	12(24)	< 0.001*
EGJ morphology	**Type I**	33(66)	43(86)	0.064
	Type II	9(18)	4(8)	
	Type III	8(16)	3(6)	
		Mean±SD	**Mean±SD**	
Age (year)		47.38±6.8	46.82±7.08	< 0.001*
IRP (mmHg)		8.06±0.76	10.14±1.51	< 0.001*
DCI (mmHg·sec·cm)		330.04±8.68	1319.44±12.33	< 0.001*
MEP (mmHg)		43.04±1.87	87.24±3.46	< 0.001*
DEP (mmHg)		42.66±2.01	65.80±2.54	< 0.001*
PEP (mmHg)		41.38±1.12	85.90±2.23	< 0.001*
LES abdominal length (cm)		1.84±0.71	2.94±0.65	< 0.001*
LESL (mmHg)		3.06±0.42	4.03±0.34	< 0.001*
LESP (mmHg)		17.20±1.10	20.56±1.78	< 0.001*
UESP (mmHg)		64.84±8.42	98.60±11.60	< 0.001*

IEM: Ineffective oesophageal motility; IRP: Integrated relaxation pressure; DCI: Distal contractile integral; MEP: Middle esophageal pressure; DEP: distal esophageal pressure; PEP: proximal esophageal pressure; LES: Lower esophageal sphincter; LESP: Lower esophageal sphincter basal pressure; LESL: Lower esophageal sphincter length; UESP: Upper esophageal sphincter basal pressure; *Significant at *P*<0.001

Table 3. Endoscopy findings and MII-pH monitoring parameters between RGERD patients with IEM and normal esophageal motility (n=100)

		IEM (n=50)	Normal (n=50)	*P*
		n (%)	n (%)	
Upper endoscopy findings	**Erosive esophagitis**	30(60)	24(48)	0.316
	Non-erosive reflux disease	20(40)	26(52)	
Patients with abnormal reflux	**Acid reflux**	25 (50)	20(40)	0.315
	Alkaline reflux	25(50)	30 (60)	
	Weakly acid reflux	18 (36)	7(14)	0.011
	Long-term acid reflux	23(46)	10 (20)	0.006*
		Mean±SD	**Mean±SD**	
Reflux episodes	**Acid reflux**	54.58± 6.84	41.22 ±3.08	< 0.001**
	Alkaline reflux	4.78 ±1.09	3.30 ± 0.95	< 0.001**
	Weakly acid reflux	34.58 ±3.20	16.50 ±1.83	< 0.001**

IEM: Ineffective esophageal motility; MII-pH monitoring: Multichannel intraluminal impedance and pH (MII-pH) monitoring; *Significant at $P<0.01$; **Significant at $P<0.001$

Discussion

IEM is the most prevalent identified abnormality by esophageal HRM (25). Nevertheless, the relationship between esophageal symptoms and esophageal hypomotility is still debatable, which leads to an uncertain diagnostic entity (26). IEM is often found in patients with a diversity of esophageal symptoms, especially dysphagia and GERD symptoms, but they are not discriminative of IEM (26,27). It has been indicated that various factors in upper gastrointestinal motility can influence GERD, particularly TLESRs, which is the most frequent cause of reflux in GERD patients (28). Furthermore, esophageal hypomotility is more common in the pH test for GERD (29). In RGERD patients, the characteristics of IEM have not been well described (13).

In this study, 50% of patients had IEM, and there were no patients with severe disorders of esophageal motility, which was consistent with the result of a study in China (13). In that study, large peristaltic breaks were found among 7.5% of wet swallows, and 50% of patients had IEM (13). There were more RGERD patients in the IEM group with long-term and weak acid reflux compared with the non-IEM group, which was similar to the present study. It was also indicated that patients with more abnormal gastroesophageal peristalsis had worse reflux (13). In another study, GERD patients with IEM had longer and more frequent reflux episodes, slower esophageal acid clearance, and longer esophageal acid exposure in comparison with non-IEM patients (30).

There were no significant differences between the mean episodes of acid or alkaline reflux among IEM and non-IEM groups in this study. Former studies had indicated that RGERD was more strongly associated with weakly alkaline and acid reflux than acid reflux (31,32). Moreover, long-term PPI therapy might decrease the identifiable differences in acid reflux episodes between IEM and non-IEM groups (13).

Overall, the findings of this study indicated that LESL, LESP, UESP, PEP, MEP, DEP, DCI, and IRP among the IEM group were significantly lower than the non-IEM group with normal esophageal motility. Fifty-four patients had erosive esophagitis. There were significant mean episode differences in acid, alkaline, and weakly acid reflux between the two groups. In another study, impaired esophageal clearance of refluxate due to ineffective peristalsis has also been detected among more patients with erosive esophagitis than those with non-erosive reflux disorder, which was in line with the findings of the present study (33).

A study declared that increased GERD symptom severity and erosive esophagitis are related to a higher probability of IEM, even though the incidence of IEM in physiologic acid exposure and non-erosive reflux disease is low (34). Moreover, severe IEM, with more than 70% ineffective peristalsis, offers helpful evidence for increased acid exposure in the supine position among those with severe GERD phenotype (35). It has been stated that esophageal hypomotility might be caused by elevated reflux exposure (26) and successful anti-reflux therapy may improve esophageal dysmotility (36). The findings of the current study propose a possible role for IEM in the pathophysiology of RGERD.

It was assumed that the IEM occurrence rises with GERD severity (13). Increased gastric reflux can lead to decreased esophageal adaptation and increased resistance throughout bolus transmission with subsequent delayed bolus transport (37). Furthermore, IEM might be partially associated with esophageal mucosal damage and be related to esophageal clearance and impaired esophageal

bolus transit (38); however, it may be more complex in patients with RGERD (13).

In a study on the durability of esophageal motor disorders based on HRM, PPI therapy was not related to better improvement in esophageal hypomotility (39). Prolonged PPIs usage may improve the symptoms of patients with RGERD, but it might decrease esophageal inflammation and lead to negative endoscopic results.

Nevertheless, there were some limitations in this study. It had a retrospective design, and it was not possible to collect sufficient data such as BMI, smoking, the severity of reflux symptoms, and detailed drugs apart from PPI. In addition, all collected data was from one clinical center, and the number of RGERD patients was limited.

IEM still leftovers an under-treated and under-recognized condition. Very few studies have illustrated IEM in patients with RGERD, and data still are not reliable to answer whether the occurrence of IEM is a secondary or primary impairment throughout the RGERD progression. There is a challenge to ordering effective therapies for patients with persistent RGERD. Further studies are necessary to explore effective treatment to improve reflux symptoms and restore normal esophageal peristalsis in RGERD patients with IEM.

In summary, the current study used HRM and MII-pH testing among patients with RGERD to evaluate the similarities and differences in RGERD patients with or without IEM. Overall, the findings of this study indicated that HRM metrics in IEM patients were significantly lower than those in the non-IEM group. IEM was related to more long-term and abnormal, weak acid reflux. It seems that the evaluation of reflux parameters and esophageal motility could lead to additional insights into the pathophysiological mechanisms of RGERD. Nevertheless, further studies are suggested to assess the effects of esophageal dysmotility among patients with RGERD.

Acknowledgments

AB, SA, and MZ conceptualized the study design. AB collected the data. SM prepared the initial draft of the manuscript and analyzed the data. All authors critically reviewed the manuscript.

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