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Impaired Esophageal Bolus Transit in Patients with Gastroesophageal Reflux Disease and Abnormal Esophageal Acid Exposure

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Background/Aims: We assessed the bolus transit and motility characteristics in gastroesophageal reflux disease (GERD) patients with abnormal esophageal pH monitoring. **Methods:** We retrospectively reviewed the combined impedance-esophageal manometry data from consecutive patients who had abnormal acid exposure during 24-hour esophageal pH monitoring. We compared these data to the results from functional heartburn (FH) and asymptomatic volunteers. **Results:** The data from 33 GERD patients (mean age of 51 years, 18 males), 14 FH patients (mean age of 51 years, one male), and 20 asymptomatic volunteers (mean age of 27 years, nine males) were analyzed. Ineffective esophageal motility was diagnosed in 10% of the volunteers, 21% of the FH patients, and 15% of the GERD patients. Ineffective contraction was more frequent in GERD and FH patients than in volunteers (16% and 20% vs 6%, respectively; $p<0.05$). Additionally, 10% of the volunteers, 21% of the FH patients and 36% of the GERD patients had an abnormal bolus transit. Complete bolus transit was less frequent, and bolus transit was slower in GERD patients than in volunteers for liquid (70% vs 85%) and viscous swallows (57% vs 73%). A longer acid clearance time was associated with abnormal bolus transit in the GERD group. **Conclusions:** Patients with GERD have mild peristaltic dysfunction and incomplete and slower esophageal bolus transit. These conditions predispose them to prolonged acid contact with the esophagus. **(Gut Liver 2012;6:440-445)**

Key Words: Gastroesophageal reflux; Bolus transit; Impedance

INTRODUCTION

Esophageal motility disturbance has been regarded as main pathophysiologic mechanism of gastroesophageal reflux disease (GERD),[1] however, manometry findings were often normal in patients with GERD. Most common pattern of peristaltic failure is ineffective esophageal motility (IEM) which is commonly associated with delayed acid clearance.[2] In a subgroup of patients with nonerosive reflux disease (NERD) or mild esophagitis, acid clearance is prolonged in spite of normal or minimally impaired esophageal peristalsis.[3]

Several studies about esophageal bolus transit of patients with GERD have reported contradictory results.[4-6] In a study with patients with reflux esophagitis, there was a marked delay in esophageal transport with increasing viscosity of the bolus. A significant delay of bolus transport in the inflamed esophageal areas was also seen.[4,5] In the other esophageal impedance study with patients with mild esophagitis, overall most swallows were considered normal.[6] A recent study reported abnormal bolus transit and esophageal motility abnormalities increase in parallel with the severity of GERD from NERD to erosive esophagitis and Barrett's esophagus.[7]

Esophageal acid clearance is composed of esophageal volume clearance, followed by chemical clearance of saliva ingestion. Combined intraluminal esophageal impedance-esophageal manometry (MII-EM) provides clinically important information about esophageal function abnormalities.[8] Impedance technique to measure esophageal volume clearance was validated compared with barium emptying.[3] Impedance could provide physiologically and clinically relevant information in GERD patients with abnormal acid exposure.[9]

Patients with abnormal acid exposure are easily supposed to have abnormal esophageal volume clearance and/or abnormal

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esophageal bolus transit. We aimed to evaluate the characteristics of esophageal bolus transit and motility of GERD patient with abnormal acid exposure compared with functional heartburn (FH) and normal volunteers with combined MII-EM.

MATERIALS AND METHODS

1. Asymptomatic volunteers

Twenty asymptomatic volunteers were recruited through an advertisement for other study in 2006.[10] None of the subjects had gastrointestinal symptoms or a history of gastrointestinal surgery except appendectomy, and none were taking any medication. It was confirmed that no subjects had any history of cardiovascular, respiratory, neuropsychiatric, or endocrine disorders. Alcohol, smoking, and medications known to influence the gastrointestinal motility were prohibited during combined MII-EM study.

2. GERD and FH patients

The consecutive patients who had visited Seoul St. Mary's Hospital with typical or atypical GERD symptoms and underwent combined MII-EM and 24-hour esophageal pH monitoring from 2007 to 2010 were enrolled. Combined MII-EM was done prior to 24-hour esophageal pH monitoring to identify the location of lower esophageal sphincter (LES). Esophageal pH monitoring was performed by conventional or impedance monitoring. Antisecretory agents including proton pump inhibitors and medications affecting esophageal motility were discontinued within 1 week before combined MII-EM and esophageal pH monitoring. All patients underwent endoscopy. Abnormal esophageal acid exposure was defined as % time pH <4 was >4 in the 24-hour esophageal conventional or impedance pH monitoring. Among them, patients who were diagnosed to have abnormal acid exposure were classified as GERD group. Patients whose principal symptom was heartburn and esophageal pH showed normal esophageal acid exposure, negative symptom index and negative symptom association analysis were classified as FH group.

3. Esophageal function test (combined MII-EM)

The nine-channel combined MII-EM catheter (Sandhill EFT; Sandhill Scientific Inc., Highland Ranch, CO, USA) has two circumferential solid-state pressure sensors, at 5 and 10 cm from the tip, and two uni-directional pressure sensors, at 15 and 20 cm. The impedance measuring segments consist of pairs of metal rings placed 2 cm apart, centered at 10, 15, 20, and 25 cm from the tip. The catheter was inserted transnasally into the esophagus to a depth of 60 cm. The LES was identified by using a stationary pull-through technique, and the most distal part of the sensor was placed in the high-pressure zone of the LES. In the semi recumbent position, patients were administered 10 swallows of 5 mL of normal saline and 10 swallows of 5 mL of viscous (apple sauce-like consistency) material, with each swallow being taken 20 to 30 seconds apart. Normal saline was used instead of water because it has a standardized ionic concentration and provides for better impedance changes than water. Sandhill Scientific Inc. provided us with the viscous material manufactured as a food substance with a known standardized impedance value.

4. Data analysis

We reviewed the data of combined MII-EM data of GERD, FH patients, and asymptomatic volunteers. We also reviewed esophageal pH monitoring data and endoscopic results of patients group.

Manometric parameters included: 1) distal esophageal amplitude as average of contraction amplitude at 5 and 10 cm above the LES, 2) mid-respiratory resting pressure, and 3) residual LES pressure during swallowing were used to assess LES function. A swallow was considered normal if contraction amplitudes at 5 and 10 cm above LES were each 30 mm Hg and distal onset velocity was <8 cm/sec. A swallow with ineffective contraction was defined if either of the contraction amplitudes at 5 and 10 cm above LES was less than 30 mm Hg, while that with simultaneous contractions was identified if contraction amplitudes at 5 and 10 cm above LES were each greater than or equal to 30 mm Hg and distal onset velocity was greater than 8 cm/sec. Subjects with 30% or more ineffective or 20% or more simultaneous contractions were considered to have abnormal esophageal manometry.

MII parameters analyzed included bolus entry at each specific level obtained at the 50% point between 3 seconds pre-swallow impedance baseline and impedance nadir during bolus presence and bolus exit determined as return to this 50% point on the impedance-recovery curve. Total bolus transit time (TBTT) was calculated as time elapsed between bolus entry at 20 cm above LES and bolus exit at 5 cm above LES. Swallows were classified by MII as showing: 1) complete bolus transit, if bolus entry occurred at the most proximal site (20 cm above LES) and bolus exit points were recorded in all three distal impedance-measuring sites (i.e., 15, 10, and 5 cm above the LES); and 2) incomplete bolus transit, if bolus exit was not identified at any one of the three distal impedance-measuring sites. Using impedance criteria, normal esophageal bolus clearance can be defined as complete clearance of at least 80% of liquid boluses and at least 70% of viscous.

5. Statistical analysis

Manometric data were described by mean±standard deviation. Descriptive statistics (median, 25th to 75th percentile) were used to describe the impedance findings because they were not normally distributed. One way ANOVA test was used to assess differences in manometric and impedance parameters among the asymptomatic volunteers, FH and GERD patients in the liquid

and the viscous swallows. The TBTT of swallows with incomplete bolus transit was regarded as an infinite value, and they were analyzed together with the TBTT of swallows with complete transit. For statistical significance, the alpha was set at 0.05.

RESULTS

The data of 33 patients with GERD (mean, 51±14 years old; M:F=18:15), 14 FH (mean, 51±10 years old; M:F=1:13), and 20 asymptomatic volunteers (mean, 27±6 years old; M:F=9:11) were analyzed. Body mass index was not different in the both groups. The predominant symptoms of GERD patients were heartburn (n=3), regurgitation (n=3), epigastria pain (n=4), globus (n=18), acid regurgitation+globus (n=3), Chronic cough (n=1), and voice change (n=1). Four the GERD patients had hernia from endoscopy.

Table 1. Baseline Characteristics of the GERD Group, FH Group, and Asymptomatic Volunteers

Characteristic	Asymptomatic volunteers (n=20)	FH (n=14)	GERD (n=33)
Age, yr	27±6	51±10	51±14
Male:Female	9:11	1:13	18:15
Body mass index, kg/m^2	21.5±3.4	21.0±1.8	22.6±2.0
Hiatal hernia		2	4
Erosive esophagitis		0	5
LA A/LA B			3/2
Nonerosive reflux disease		0	28
% Total time pH <4		1.3±0.8	7.4±3.9
DeMeester score		5.83±3.0	25.3±13.4

Data are presented as mean±SD or number.
GERD, gastroesophageal reflux disease; FH, functional heartburn; LA, Los Angeles classification.

In accordance with the LA classification, there were three patients with grade A esophagitis and 2 patients with grade B esophagitis. Others didn't have esophageal erosion. Viscous swallow was not performed in six GERD patients and three FH patients because of absence of the viscous material. Mean percentage time of pH <4 was 7.4±3.9% in GERD group (Table 1).

1. Manometric parameters of GERD, FH, and asymptomatic volunteers

The manometric diagnoses of GERD group were normal in 25, IEM in five and nutcracker esophagus in three patients. The IEM was diagnosed in 10% of normal volunteers, 21% of FH and 15% of GERD patients (p>0.05). Mid-respiratory basal LES pressure was lowest in GERD patients and it was significantly lower in FH compared to volunteers. The distal esophageal contraction amplitude was not different among three groups (Table 2).

Three hundred thirty-five liquid swallows and 265 viscous swallows in GERD group, 140 liquid swallows and 110 viscous

Table 2. Manometric Parameters and Esophageal Contraction Patterns in the GERD Group, FH Group, and Asymptomatic Volunteers

Parameter	Asymptomatic volunteers (n=20)	FH (n=14)	GERD (n=33)	p-value
Manometric diagnosis (liquid)				
Normal	16 (80)	11 (79)	25 (76)	NS
Ineffective esophageal motility	2 (10)	3 (21)	5 (15)	
Nutcracker esophagus	2 (10)	0	3 (9)	
Mean basal LES pressure, mm Hg*	28.3±8.7	22.2±11.3	17.9±12.6	<0.05
Residual LES pressure, mm Hg	2.8±4.2	1.7±3.3	1.7±6.8	NS
Distal esophageal contraction amplitude, mm Hg				
Liquid swallows	107.4±46.5	108.8±50.0	100.6±51.7	NS
Viscous swallows	100.0±47.7	93.9±56.3	90.9±46.0	NS
No. of liquid swallows	200	140	335	
Peristalsis (liquid swallows)				
Swallow with normal contraction	189 (95)	127 (91)	300 (90)	NS
Swallow with ineffective contraction	11 (6)	13 (9)	35 (10)	NS
No. of viscous swallows	197	110	265	
Peristalsis (viscous swallows)				
Swallow with normal contraction†	180 (95)	88 (80)	222 (84)	<0.05
Swallow with ineffective contraction†	11 (6)	22 (20)	43 (16)	<0.05

Data are presented as number (%) or mean±SD .
GERD, gastroesophageal reflux disease; FH, functional heartburn; NS, not significant; LES, lower esophageal sphincter.
*p<0.05, asymptomatic volunteers vs FH or GERD group and FH group vs GERD group; †p<0.05, asymptomatic volunteers vs FH or GERD group.

Table 3. Impedance Parameters for the GERD Group, FH Group, and Asymptomatic Volunteers

Parameter	Asymptomatic volunteers	FH	GERD	p-value
Liquid				
Patients with abnormal bolus transit, %	10 (2/20)	29 (4/14)	36 (12/33)	NS
Complete bolus transit rate, %				
All swallow*	85 (170/200)	88 (123/140)	70 (233/335)	<0.01
Swallow with normal contraction*	89 (168/189)	94 (119/127)	74 (223/300)	<0.01
TBTT, median (25-75th percentile), sec				
All swallow*	6.4 (5.8–7.8)	7.2 (6.4–8.2)	7.1 (5.7–>12.5)	<0.01
Swallow with normal contraction*	6.4 (5.8–7.8)	7 (6.4–7.7)	6.9 (5.6–>12.5)	<0.01
Viscous				
Patients with abnormal bolus transit, %	35 (7/20)	27 (3/11)	55 (15/27)	NS
Complete bolus transit rate, %				
All swallow*	73 (147/197)	72 (80/110)	57 (152/265)	<0.01
Swallow with normal contraction*	81 (146/180)	85 (75/88)	66 (147/222)	<0.01
TBTT, median (25-75th percentile), sec				
All swallow*	8.1 (7.2–>12.5)	8.7 (7.0–12.5)	9.6 (7.4–>12.5)	<0.01
Swallow with normal contraction*	8.0 (7.1–10.2)	8.2 (6.9–>9.5)	8.2 (7.1–>12.5)	<0.01

TBTT, >12.5 means 'infinite' in swallows with an incomplete bolus transit.
GERD, gastroesophageal reflux disease; FH, functional heartburn; NS, not significant; TBTT, total bolus transit time.
*p<0.05, GERD group vs asymptomatic volunteers or FH group.

swallows in FH group and 200 liquid swallows and 197 viscous swallows in asymptomatic volunteers were analyzed. Most of liquid swallows in all groups showed normal peristaltic contraction. GERD patients showed less frequent normal peristaltic contractions in the viscous swallows, compared to FH patients and asymptomatic volunteers (5% vs 20% and 16%, p<0.05). The frequency of normal peristaltic contractions in viscous swallows was not different between other two groups.

2. Impedance parameters of GERD, FH, and asymptomatic volunteers

IEM was diagnosed in 10% of asymptomatic, 21% of FH, and 15% of GERD patients. Incomplete bolus transit was more frequent and bolus transit was slower in GERD patients than volunteers in liquid (bolus transit rate, 70% vs 85%; median TBTT, 7.1 seconds [5.7 to >12.5] vs 6.4 seconds [5.8 to 7.8]) and viscous swallows (bolus transit rate, 57% vs 73%; median TBTT, 9.6 seconds [7.4 to >12.5] vs 8.1 seconds [7.2 to >12.5]). Bolus transit rate and TBTT were not different between asymptomatic volunteers and FH patients (Table 3).

3. Manometric and impedance parameters of erosive reflux disease (ERD) and NERD

The manometric and impedance data were reanalyzed according to the esophageal erosion. The basal LES pressure, distal esophageal contraction amplitude, viscous bolus transit parameters were not different in both groups (Table 4). However, TBTT in ERD group was significantly longer than NERD group in the liquid swallows (Table 5).

Table 4. Manometric Parameters for the ERD Group and NERD Groups

Parameter	ERD (n=5)	NERD (n=28)	p-value
Manometric diagnosis (liquid)			
Normal	2	23	NS
Ineffective esophageal motility	2	3	
Nutcracker esophagus	1	2	
Basal LES pressure, mm Hg	12.4±10.4	18.9±12.5	NS
Residual LES pressure, mm Hg	-1.1±7.0	2.2±6.7	NS
% Total time pH <4	6.4±1.8	7.6±4.1	NS
DeMeester score	23.3±8.7	25.6±14.2	NS
Distal esophageal contraction amplitude, mm Hg			
Liquid swallows	107.8±67.0	99.7±50.9	NS
Viscous swallows	113.2±75.8	83.5±36.2	NS

Data are presented as number or mean±SD.
ERD, erosive reflux disease; NERD, nonerosive reflux disease; NS, not significant; LES, lower esophageal sphincter.

4. Correlation between bolus transit parameters and 24-hour esophageal pH parameters

Bolus transit parameters of individual swallow were not correlated with any parameters of 24-hour pH monitoring, such as % time pH <4, DeMeester score, longest time of reflux except acid clearance time. Acid clearance time was longer in GERD

patients who had abnormal bolus transit than GERD patients with normal bolus transit in liquid swallows (1.4±1.3 seconds vs 1.2±0.6 seconds, p<0.05) and viscous swallows (1.3±1.2 seconds vs 1.1±0.4 seconds, p<0.05) (Fig. 1).

DISCUSSION

In this study, we found that patients with GERD frequently had incomplete or slow bolus transit compared to asymptomatic volunteers and FH patients. Our findings suggested that abnormal esophageal transit was a common pathophysiologic abnormality of GERD and might cause delayed esophageal volume clearance and esophageal erosions. GERD patient who had abnormal bolus transit had longer acid clearance time. These findings also suggested bolus transit abnormality would influence the prolonged acid contact. Abnormal transit underlies prolonged acid clearance by affecting esophageal emptying and saliva transport.

Table 5. Impedance Parameters for the ERD Group and NERD Groups

Parameter	ERD	NERD	p-value
Liquid			
Patients with abnormal bolus transit, %	60 (3/5)	32 (9/28)	NS
Complete bolus transit rate, %	66 (33/50)	70 (199/285)	NS
TBTT, median (25-75th percentile), sec	8.1 (6.8->12.5)	6.9 (5.6->12.5)	0.02
Viscous			
Patients with abnormal bolus transit, %	40 (2/5)	45 (10/22)	NS
Complete bolus transit rate, %	56 (28/50)	54 (116/215)	NS
TBTT, median (25-75th percentile), sec	8.8 (7.4->12.5)	10.6 (7.5->12.5)	NS

TBTT, >12.5 means 'infinite' in swallows with incomplete bolus transit.
ERD, erosive reflux disease; NERD, nonerosive reflux disease; NS, not significant; TBTT, total bolus transit time.

The abnormal bolus transit was frequently observed in GERD patients 36% and 55% of in liquid and viscous swallows, respectively. As expected, patients with esophageal erosion had prolonged bolus transport. It is conceivable that the inflamed esophageal mucosa as one of the results of impaired bolus transit. The prevalence of abnormal transit in NERD patients was higher than previous studies in which demonstrated minimal transit abnormalities in NERD patients.[4] This discrepancy might be related to the fact that we enrolled only patients who were confirmed as having abnormal acid exposure by 24-hour pH monitoring.

This study showed mild peristaltic dysfunction and lower LES pressure in GERD patients. Peristaltic dysfunction may be involved in impaired esophageal propulsion mechanisms and prolonged esophageal clearance.[10] Mean basal LES was lowest in the GERD groups and it was lower in FH compared to volunteers, although these results were still within the normal range. Ineffective peristaltic contraction was not different in liquid swallows, but more frequent in viscous swallows in GERD group compared with other groups. Viscous swallows are more sensitive than liquid swallows to detect motor or bolus transit abnormality. In the present study, the prevalence of IEM was similar among patients with GERD, FH, and asymptomatic volunteers, the reason of that is because most of enrolled patients were NERD and other patients were mild reflux esophagitis.

The esophageal motility and bolus transit patterns of FH were interesting. The esophageal bolus transit pattern of FH patients was similar as healthy volunteers, rather than GERD. However, the motility abnormality is distinct from volunteers. Mean LES pressure was lower and ineffective contraction in viscous swallows was more frequent in FH than volunteers. Their esophageal

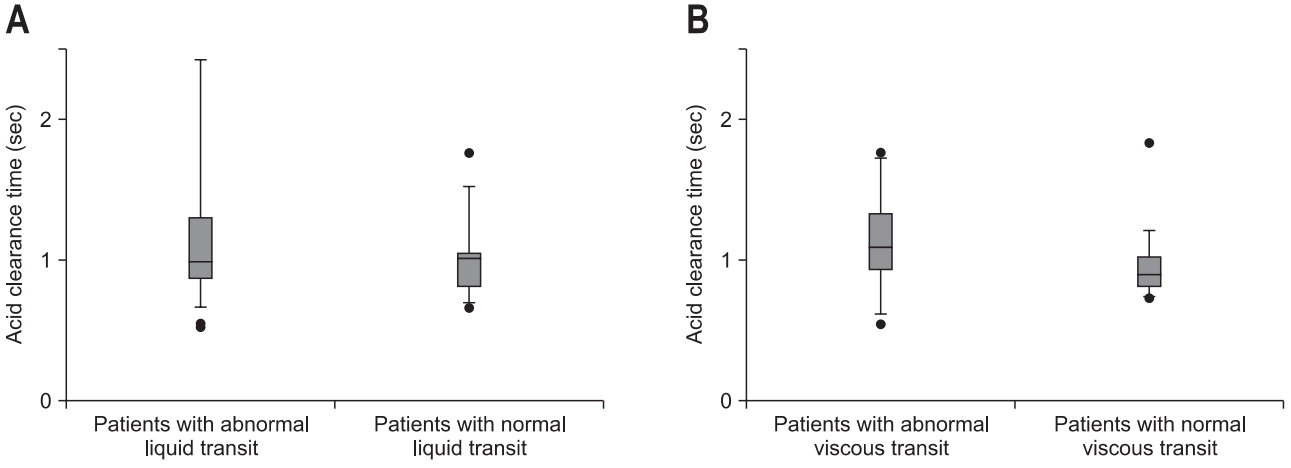

Fig. 1. Acid clearance time according to bolus transit abnormality in patients with gastroesophageal reflux disease. (A) Liquid swallows. (B) Viscous swallows.

motility abnormality seems to be between asymptomatic volunteers and GERD. These results also support the exclusion of FH from real GERD with abnormal pH acid exposure.

From the results of this study, abnormal transit could be as a biomarker for clinical trial in patients with GERD. Outcome data would be needed to evaluate the prognostic value of combined MII-EM in patients with GERD during therapeutic trial. Also, the results of this study suggest the therapeutic possibility of prokinetics even in GERD patients with normal manometric findings.

There are some limitations in this study. First, the asymptomatic volunteers were not age, sex-matched control and were not recruited during the same study period. Strictly saying, abnormal bolus transit was also observed in the control group, although infrequently. It suggests the asymptomatic control groups might not represent true normal subject. Second, the number of patients with ERD was too small to characterize the bolus transit in these patients. However, the present study has some strength. The GERD group was homogenous. All of the patients had abnormal esophageal exposure irrespective of symptom association.

In conclusion, GERD patients with abnormal acid exposure were characterized by mild peristaltic dysfunction, lower LES pressure, and delayed and frequent abnormal esophageal bolus transit. It suggests that peristaltic dysfunction and functional defects in these patients predispose them to prolonged acid contact in the esophagus.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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