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Original Article

Transient Hiatal Separation During Straight Leg Raise Can Predict Reflux Burden in Gastroesophageal Reflux Disease Patients With Ineffective Esophageal Motility

Wei-Yi Lei,[1] Shu-Wei Liang,[1] Taher Omari,[2] Wei-Chuan Chang,[3] Ming-Wun Wong,[1] Jui-Sheng Hung,[1] Chih-Hsun Yi,[1] Tso-Tsai Liu,[1] Lin Lin,[1] C Prakash Gyawali,[4] and Chien-Lin Chen[1,5*]

[1]Department of Medicine, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation and Tzu Chi University, Hualien, Taiwan; [2]College of Medicine and Public Health Flinders University, Adelaide, Australia; [3]Department of Medical Research, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Hualien, Taiwan; [4]Division of Gastroenterology, Washington University School of Medicine, St Louis, MO, USA; and [5]Institute of Medical Sciences, Tzu Chi University, Hualien, Taiwan

Background/Aims
Straight leg raise (SLR) can be utilized to evaluate the integrity of the esophagogastric junction during high-resolution manometry (HRM). We aim to assess the value of transient hiatal separation during SLR in symptomatic reflux patients.

Methods
Consecutive reflux patients undergoing esophageal HRM and pH monitoring were included. Transient hiatal separation was defined by a ≥ 1 cm separation between the lower esophageal sphincter and crural diaphragm during SLR. We compared esophageal motor patterns and reflux monitoring parameters between patients with normal, transiently abnormal and consistently abnormal esophagogastric junction morphology during SLR.

Results
Of 85 (56.3% female, mean age: 46.7 ± 12.3 years) completed SLR, esophagogastric junction morphology was normal in 31 (36.5%), transient hiatal separation in 19 (22.3%), and consistently hiatal hernia in 35 (41.2%). The values of total acid exposure time (P = 0.016), longest acid reflux episodes (P = 0.024), and DeMeester scores (P = 0.016) were higher in hiatal hernia compared to patients with non-transient hiatal separation, but there were no differences between those with and without transient hiatal separation. Within ineffective esophageal motility, the presence of transient hiatal separation during SLR significantly associated with a higher total acid exposure time (P = 0.014), higher DeMeester scores (P = 0.019), higher total acid reflux events (P = 0.037), and higher longest acid reflux episodes (P = 0.006).

Conclusion
Our work suggests that SLR may have value as a provocative test during HRM, and future outcome studies are warranted to elucidate the clinical relevance of motor abnormalities depicted from SLR.
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Key Words
Esophageal sphincter, lower; Hernia, hiatal; Leg; Manometry

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*Correspondence: Chien-Lin Chen, MD, PhD
Department of Medicine, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation and Tzu Chi University, 707, Section 3, Chung-Yang Road, Hualien, Taiwan
Fax: +88-638561825, E-mail: harry.clchen@msa.hinet.net

Introduction

Gastroesophageal reflux disease (GERD) is a common condition with multifactorial pathogenesis. Key mechanisms of GERD include abnormal esophagogastric junction (EGJ) morphology and function, and esophageal body hypomotility.[1,2] High-resolution manometry (HRM) has expanded evaluation of esophageal motor function to include EGJ morphology, which contributes to pathophysiologic mechanisms underlying GERD.[3,4] The lower esophageal sphincter (LES) and crural diaphragm (CD) together form the EGJ, which serves as a barrier between the esophagus and the stomach, and plays a major role in reflux prevention.[5] Disrupted EGJ morphology and reduced EGJ resting tone associate with abnormal acid burden in GERD.[6,7] Additionally, esophageal hypomotility such as ineffective esophageal motility (IEM) can impair esophageal bolus clearance and contribute to abnormally high reflux burden.[2,8] However, the current standard HRM protocols are based on small volume water swallows, which may not explain the causes of esophageal symptoms or detect clinically relevant motor abnormalities.[9]

Adjunctive provocative maneuvers such as multiple rapid swallows (MRS), and rapid drink challenge can augment the diagnostic yield of HRM by uncovering otherwise unrecognized motor abnormalities.[10] Artificially increasing intra-abdominal pressure applies physiologic stress to the EGJ, and has been utilized as a provocative maneuver during HRM to evaluate EGJ barrier function. Abdominal compression with binders, Valsalva maneuvers, and straight leg raise (SLR) can evaluate whether increased intra-abdominal pressure is transmitted into the intra-thoracic cavity through a defective EGJ.[11-14] Rogers et al[14] recently demonstrated that measurement of trans-EGJ pressure gradient during SLR can assess integrity of the EGJ barrier, and suggested that analysis of intra-esophageal pressure gradients during SLR can provide adjunctive evidence of pathologic GERD.[15] However, the clinical impact of transient SLR induced hiatal separation on esophageal acid burden remains unknown.

The aim of this study is to examine the effect of transient hiatal separation during SLR maneuver on esophageal acid burden in symptomatic GERD patients. We hypothesized that transient hiatal separation during SLR would be associated with higher acid burden in the distal esophagus compared to no separation. We also evaluated differences in the transient hiatal separation response between IEM and normal esophageal motility.

Materials and Methods

Study Population

We prospectively enrolled consecutive adult patients referred for esophageal physiological testing for evaluation of GERD symptoms between May 2019 and October 2020. For inclusion, all patients required to have undergone upper endoscopy, HRM with successful completion of the SLR maneuver, as well as ambulatory reflux monitoring. Exclusion criteria consisted of previous foregut surgery, esophageal neoplasia or stricture, eosinophilic esophagitis, major esophageal motility disorders, or unsuccessful SLR maneuver. Demographic information, medication history and clinical presentation were extracted from the medical records. All patients completed validated GERD questionnaires including Reflux Disease Questionnaire (RDQ), GERD Questionnaire, and Reflux Symptom Index (RSI) identifying dominant symptoms before undergoing upper gastrointestinal endoscopy and esophageal physiologic evaluation.

The RDQ consists of 12 items for measuring the frequency, severity and duration of three dimensions including heartburn, regurgitation and dyspepsia. The mean of all 3 dimensions provides a total score ranging from 0 to 5. Any individual with RDQ score ≥ 3 in either heartburn or regurgitation dimensions was defined as having GERD.[16] The GERD Questionnaire is composed of 6 questions to assess the impact of GERD on patient's lives and to measure response to treatment over time. It includes 6 items regarding the frequency of GERD symptoms in the last week, each with 5 response options ranging from 0 to 3, with higher scores denoting more symptoms.[17] The RSI consists of 9 questions related to reflux symptoms. The severity of each symptom ranges from 0 to 5 points for severity of symptoms. Patients with sum of RSI score greater than 13 were considered to have laryngopharyngeal reflux.[18]

During the endoscopic examination, presence of hiatal hernia and mucosal injury in the distal esophagus was recorded. All patients provided informed consent prior to participation in this study. The study protocol was approved by the Research Ethics Committee (Approval No. IRB109-012-A), confirming that the study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki.

Esophageal High-resolution Manometry

Following an overnight fast, a 36-channel solid-state catheter system with circumferential sensors at 1-cm intervals (MMS, Enschede, The Netherlands) was passed trans-nasally under topical anesthesia by an experienced nurse, and positioned with the 3 distal-most sensors in the stomach.[4] Medications that would affect esophageal motor function were asked to be discontinued 1 week prior to the study. The HRM protocol consisted of a 5-minute baseline recording, followed by 10 swallows of 5 mL of room temperature water at 20-30 second intervals in a supine, semi-recumbent position. Provocative testing with at least 3 MRS sequences was performed using 5 swallows of 2 mL of water every 2-3 seconds in the supine position.[19,20] Standard HRM metrics including integrated relaxation pressure (IRP), distal contractile integral (DCI), and distal latency were used for characterization of esophageal body contraction and peristaltic function according to Chicago classification version 4.0 (CCv4.0).[21] Data from HRM studies were analyzed using a proprietary software (MMS Database software), after thermal compensation was applied to each study.

Peristaltic breaks which were identified using a 20 mmHg isobaric contour were measured using software tools.[22] Each swallow was characterized as intact, weak, or failed contraction (DCI ≥ 450 mmHg.sec.cm, 100-450 mmHg·sec·cm, or ≤ 100 mmHg·sec·cm, respectively).[22] Median IRP from supine swallows was used to assess swallow induced LES relaxation.[22] Esophagogastric junction contractile integral (EGJ-CI) was calculated to assess EGJ barrier function using methodology described elsewhere.[23] EGJ morphology was classified based on the spatial relationship between LES and CD (type 1: superimposed LES and CD, type 2: less than 3 cm separation, and type 3: ≥ 3 cm separation).[24] By using CCv4.0, IEM was defined as more than 70% ineffective swallows or at least 50% failed peristalsis.[21] MRS sequences were analyzed for complete inhibition and contractile response of esophageal body. Contractile reserve was identified when the ratio between MRS, DCI, and averaged single swallow DCI was more than 1.[19]

Straight Leg Raise Maneuver and Transient Hiatal Separation

Following the standard HRM protocol, SLR maneuver was attempted with the patient in the supine position. Patients were asked to raise their legs by flexing the hip beyond 45 degrees with the knees in extension without support for at least 5 seconds. This SLR maneuver was performed 3 times 30 seconds apart, but only 1 successful maneuver was required for data analysis. A successful SLR maneuver was defined as an increase of intra-abdominal pressure during the maneuver. In patients without hiatal hernia on the baseline HRM, the EGJ was carefully evaluated to determine whether a separation between CD and the LES developed during SLR maneuver. Transient hiatal separation was defined as a ≥ 1 cm separation between the CD and the LES during SLR maneuver, measured using on-screen software tools. All HRM images were reviewed by 2 experienced motility specialists. Any discordance in diagnosis was discussed by at least 3 experienced motility experts, and the final diagnosis was made by consensus. Figure 1 shows an example of a hiatal separation during SLR maneuver.

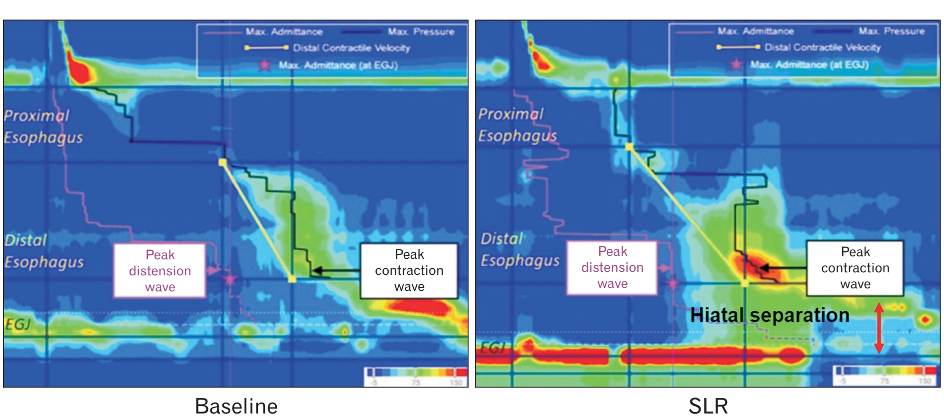

Figure 1. Example of a high-resolution manometry during straight leg raise (SLR) maneuver. During SLR intra-abdominal pressure augments with concomitant hiatal separation compared to baseline. The red double arrow indicates the length of separation between lower esophageal sphincter and crural diaphragm (swallowgateway.com). EGJ, esophagogastric junction.

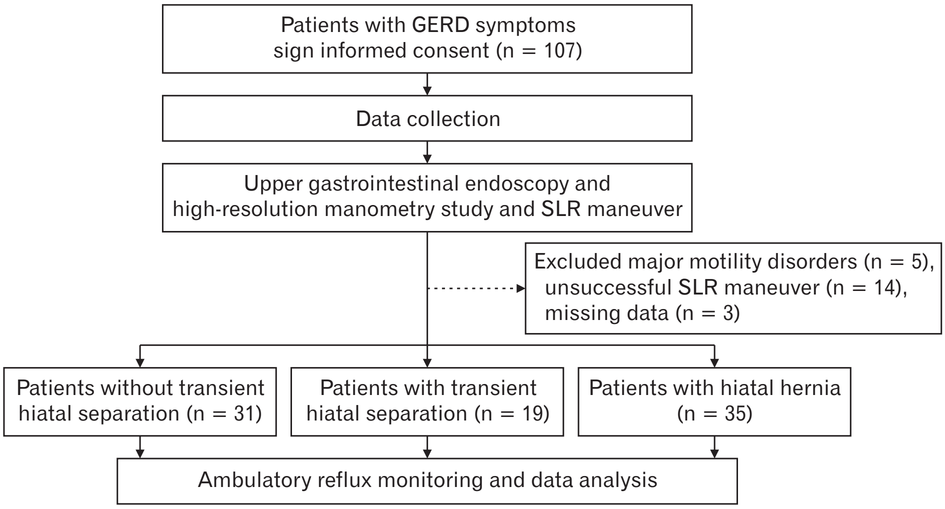

Figure 2. The flowchart of patients enrolled into the study. GERD, gastroesophageal reflux disease; SLR, straight leg raise.

Ambulatory Reflux Monitoring

Patients enrolled into this study were instructed to discontinue proton pump inhibitors 1 week prior to pH-impedance monitoring, whereas prokinetic agents, histamine-2 receptor antagonists, antacids, and anticholinergic medication were held for at least 3 days before testing. Using HRM localization of the proximal margin of the LES, the pH-impedance catheter (MMS) was inserted through the nostril and positioned with the distal pH sensor 5 cm above the proximal border of LES. Impedance was measured at 3, 5, 7, 9, 15, and 17 cm above the LES. Patients recorded activities, meals, and symptoms using standard methodology.[25] The recorded data were extracted from the pH-impedance studies, and analyzed in accordance with Lyon consensus thresholds.[3] Total acid exposure time (AET) > 6% was considered pathologic, whereas values < 4% was defined as physiologic, and values between 4% and 6% considered indeterminate.[3] Upright and supine AET was considered pathologic if value > 6% and > 2%, respectively.[3]

Statistical Methods

Continuous data were expressed as median (interquartile range), whereas categorical data were reported using frequencies and proportions. Categorical variables were compared using the chi-square test. Continuous data were analyzed using the Mann–Whitney *U* test or Kruskal-Wallis test for comparisons between groups as appropriate. Post hoc analysis was performed via Dunn correction. All analyses were performed using SPSS (version 21.0; IBM Corp, Armonk, NY, USA). A *P*-value less than 0.05 was required for statistical significance.

Results

Demographic and Clinical Characteristics

Of 107 patients who underwent HRM during the study period, 85 (56.3% female, mean age: 46.7 ± 12.3 years) successfully completed the SLR maneuver and were included in the final analysis. Of these, 50 patients (58.8%) had normal EGJ morphology, and 35 patients (41.2%) had a hiatal hernia. Among the hiatal hernia identified, 20 (57.0%) were type II and 15 (43.0%) type III EGJ. The median length of LES-CD separation was 2.6 (2.1-2.9) in type II and 3.7 (3.3-4.1) in type III. In 19 patients with normal baseline EGJ morphology (22.3%) performance of the SLR maneuver led to transient hiatal separation, whereas 31 (36.4%) patients did not demonstrate hiatal separation during SLR (Fig. 2). Thirty-four (97.1%) patients with a hiatal hernia on HRM had endoscopic defined hiatal hernia, compared to 4 (12.9%) patients in the non-transient hiatal separation group and 2 (10.5%) in the transient hiatal separation group ($P < 0.001$). In addition, patients with hiatal hernia had greater body mass index compared to those with transient hiatal separation (median [IQR]: 24.3 [22.3-26.2] kg/m^2 vs 21.6 [20.9-24.8] kg/m^2; $P = 0.041$). However, age, gender, alcohol consumption, smoking status, endoscopic findings, and GERD questionnaire responses were not different (Table 1).

High-resolution Manometry Measures of Esophageal Body and Esophagogastric Junction Function

Both standard HRM and provocative testing with MRS were completed in all patients, and findings are described in Table 2.

Table 1. Demographic Characteristics of Patients With and Without Transient Hiatal Separation During Straight Leg Raise and Hiatal Hernia

Characteristics	Non-hiatal separation (n = 31)	Transient hiatal separation (n = 19)	Hiatal hernia (n = 35)	*P*-value
Demographic factors				
Age (yr)	43.5 (30.8, 56.3)	46.0 (41.0, 55.0)	52.0 (38.0, 59.0)	0.376
Female	19 (61.3)	8 (42.1)	21 (60.0)	0.356
BMI (kg/m^2)	24.1 (22.1, 25.3)	21.6 (20.9, 24.8)	24.3 (22.3, 26.2)	0.041[a]
Smoking	2 (6.5)	1 (5.3)	5 (14.3)	0.432
Alcohol	8 (25.8)	7 (36.8)	8 (22.9)	0.533
Erosive esophagitis				0.553
Barrett's	0 (0.0)	1 (5.3)	0 (0.0)	
GERD A	4 (12.9)	3 (15.9)	8 (22.9)	
GERD B	2 (6.5)	2 (10.4)	3 (8.6)	
GERD C	0 (0.0)	1 (5.3)	1 (2.9)	
GERD D	0 (0.0)	0 (0.0)	0 (0.0)	
Normal	25 (80.6)	12 (63.1)	23 (65.7)	
Endoscopic hiatal hernia	4 (12.9)	2 (10.5)	34 (97.1)	< 0.001[b]
Questionnaire				
GERDQ score	8.0 (5.0, 12.0)	7.0 (3.0, 11.0)	8.5 (4.0, 11.0)	0.780
RDQ score	14.5 (6.8, 23.3)	17.0 (9.0, 22.0)	16.0 (9.0, 21.5)	0.848
RSI score	16.0 (13.0, 21.0)	14.0 (6.0, 21.0)	12.0 (9.0, 21.3)	0.411

[a]Indicated statistically significant between transient hiatal separation and hiatal hernia groups by post-hoc analysis via Dunn's test.
[b]Indicated statistically significant between hiatal hernia and transient or non-hiatal separation.
BMI, body mass index; GERDQ, Gastroesophageal Reflux Disease Questionnaire; RDQ, Reflux Disease Questionnaire; RSI, Reflux Symptom Index.
Data are presented as median (interquartile range: Q1, Q3) or n (%).

Table 2. High-resolution Manometric Metrics Among Patients With and Without Transient Hiatal Separation During Straight Leg Raise and Hiatal Hernia

Characteristics	Non-hiatal separation (n = 31)	Transient hiatal separation (n = 19)	Hiatal hernia (n = 35)	*P*-value
EGJ-CI	39.0 (26.0, 55.0)	37.0 (22.0, 62.0)	31.0 (16.0, 54.0)	0.212
LES resting pressure	30.9 (20.6, 43.5)	29.1 (19.7, 43.1)	22.0 (12.9, 36.2)	0.085
IRP-4s (mmHg)	9.8 (4.7, 12.6)	10.2 (4.3, 14.9)	8.5 (2.8, 13.7)	0.651
DCI (mmHg·sec·cm)	602.0 (204.0, 1030.0)	1012.0 (478.0, 1205.0)	524.0 (180.0, 917.0)	0.126
Ineffective (%)	50.0 (0.0, 90.0)	0.0 (0.0, 50.0)	50.0 (10.0, 80.0)	0.035[a]
Failed (%)	10.0 (0.0, 40.0)	0.0 (0.0, 20.0)	0.0 (0.0, 50.0)	0.247
Premature (%)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.541
Fragmented (%)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	1.000
Distal latency (sec)	6.8 (6.1, 7.7)	6.9 (6.2, 8.1)	7.2 (6.4, 8.2)	0.192
Peristaltic breaks (cm)	2.0 (0.3, 8.3)	0.9 (0.2, 2.8)	1.2 (0.3, 6.7)	0.747
Largest break (cm)	1.4 (0.1, 3.9)	0.7 (0.2, 2.3)	1.0 (0.2, 5.8)	0.926
MRS response	24 (82.2)	18 (94.7)	22 (64.7)	0.030

[a]Indicated statistically significant between transient hiatal separation and hiatal hernia groups by Dunn's test.
Statistical significance among these three groups was assessed by Kruskal-Wallis test with post hoc analysis via Dunn's test.
EGJ-CI, esophagogastric junction contractile integral; LES, lower esophageal Sphincter; IRP-4s, 4 seconds integrated relaxation pressure; MRS, multiple rapid swallow.
Data are presented as median (interquartile range: Q1, Q3) or n (%).

Table 3. Comparison of Reflux Parameters Between Patients With and Without Transient Hiatal Separation and Hiatal Hernia

Characteristics	Non-hiatal separation (n = 31)	Transient hiatal separation (n = 19)	Hiatal hernia (n = 35)	*P*-value
Time reflux pH < 4 (%)				
Total	0.8 (0.5, 2.3)	1.6 (0.9, 2.4)	2.5 (1.3, 5.8)	0.016[a]
Upright	1.3 (0.6, 3.3)	2.2 (1.3, 3.5)	4.4 (2.3, 7.5)	0.009[a]
Recumbent	0.0 (0.0, 0.1)	0.0 (0.0, 0.1)	0.0 (0.0, 0.1)	0.256
Number of acid reflux episodes				
Total	17.0 (6.0, 33.0)	22.0 (15.0, 30.0)	33.0 (12.0, 45.0)	0.145
Upright	16.0 (5.0, 30.0)	22.0 (15.0, 30.0)	32.0 (10.0, 42.0)	0.154
Recumbent	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.0 (0.0, 3.0)	0.324
Longest acid reflux episode (min)				
Total	2.6 (1.8, 4.0)	4.1 (1.4, 5.4)	5.3 (3.1, 10.8)	0.024[a]
Upright	2.6 (1.8, 3.9)	4.1 (1.4, 5.4)	5.3 (3.1, 9.0)	0.022[a]
Recumbent	0.0 (0.0, 1.1)	0.0 (0.0, 0.5)	0.0 (0.0, 3.6)	0.244
DeMeester score	3.4 (1.8, 7.5)	4.7 (3.5, 7.9)	8.4 (3.9, 16.7)	0.016[a]
Number of reflux events				
Total				
Acid	19.0 (9.0, 26.0)	26.0 (11.0, 37.0)	25.0 (13.0, 37.0)	0.144
Weakly acid	34.0 (14.0, 56.0)	20.0 (10.0, 45.0)	23.0 (16.0, 32.0)	0.303
Weakly alkaline	1.0 (0.0, 7.0)	0.0 (0.0, 1.0)	0.0 (0.0, 4.0)	0.145
Liquid	14.0 (5.0, 24.0)	11.0 (6.0, 25.0)	14.0 (8.0, 22.0)	0.968
Mixed	42.0 (25.0, 65.0)	41.0 (28.0, 63.0)	40.0 (28.0, 50.0)	0.638
Upright				
Acid	19.0 (7.0, 26.0)	26.0 (11.0, 36.0)	25.0 (12.0, 36.0)	0.152
Weakly acid	30.0 (10.0, 52.0)	19.0 (10.0, 45.0)	19.0 (14.0, 28.0)	0.399
Weakly alkaline	1.0 (0.0, 7.0)	0.0 (0.0, 1.0)	0.0 (0.0, 3.0)	0.153
Liquid	12.0 (5.0, 21.0)	10.0 (5.0, 24.0)	11.0 (6.0, 18.0)	0.997
Mixed	42.0 (24.0, 64.0)	41.0 (28.0, 63.0)	37.0 (25.0, 50.0)	0.692
Recumbent				
Acid	0.0 (0.0, 0.0)	0.0 (0.0, 1.0)	0.0 (0.0, 2.0)	0.268
Weakly acid	1.0 (0.0, 5.0)	0.0 (0.0, 3.0)	1.0 (0.0, 5.0)	0.336
Weakly alkaline	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.983
Liquid	1.0 (0.0, 4.0)	1.0 (0.0, 2.0)	1.0 (0.0, 6.0)	0.710
Mixed	1.0 (0.0, 2.0)	1.0 (0.0, 1.0)	1.0 (0.0, 2.0)	0.781

[a]Indicated statistically significant between non-hiatal separation and hiatal hernia groups.
Statistical significance among these three groups was assessed by Kruskal-Wallis test with post-hoc analysis via Dunn's test.
Data are presented as median (interquartile range: Q1, Q3) or n (%).

LES resting pressure, 4 seconds integrated relaxation pressure, EGJ-CI, DCI, distal latency, peristaltic break size, and MRS contractile responses was similar amongst those with and without transient hiatal separation, as well as patients with hiatal hernia.

Comparison of pH-Impedance Data Between the Groups

Table 3 describes a comparison of pH-impedance parameters among the groups. Patients with hiatal hernia had significantly higher median total AET (2.5 [1.3-5.8] vs 0.8 [0.5-2.3], P = 0.016) and upright AET (4.4 [2.3-7.5] vs 1.3 [0.6-3.3], P = 0.009) compared to the non-hiatal separation group. Similarly, hiatal hernia patients had more frequent median total longest acid reflux episodes (5.3 [3.1-10.8] vs 2.6 [1.8-4.0], P = 0.024) and upright longest acid reflux episodes (5.3 [3.1-9.0] vs 2.6 [1.8-3.9], P = 0.022) compared to patients in the non-hiatal separation group. DeMeester score was also significantly higher in hiatal hernia patients compared to the non-hiatal separation group (P = 0.016). No difference was observed in impedance parameters across the groups.

Of 20 patients with IEM, 8 patients' performance of the SLR

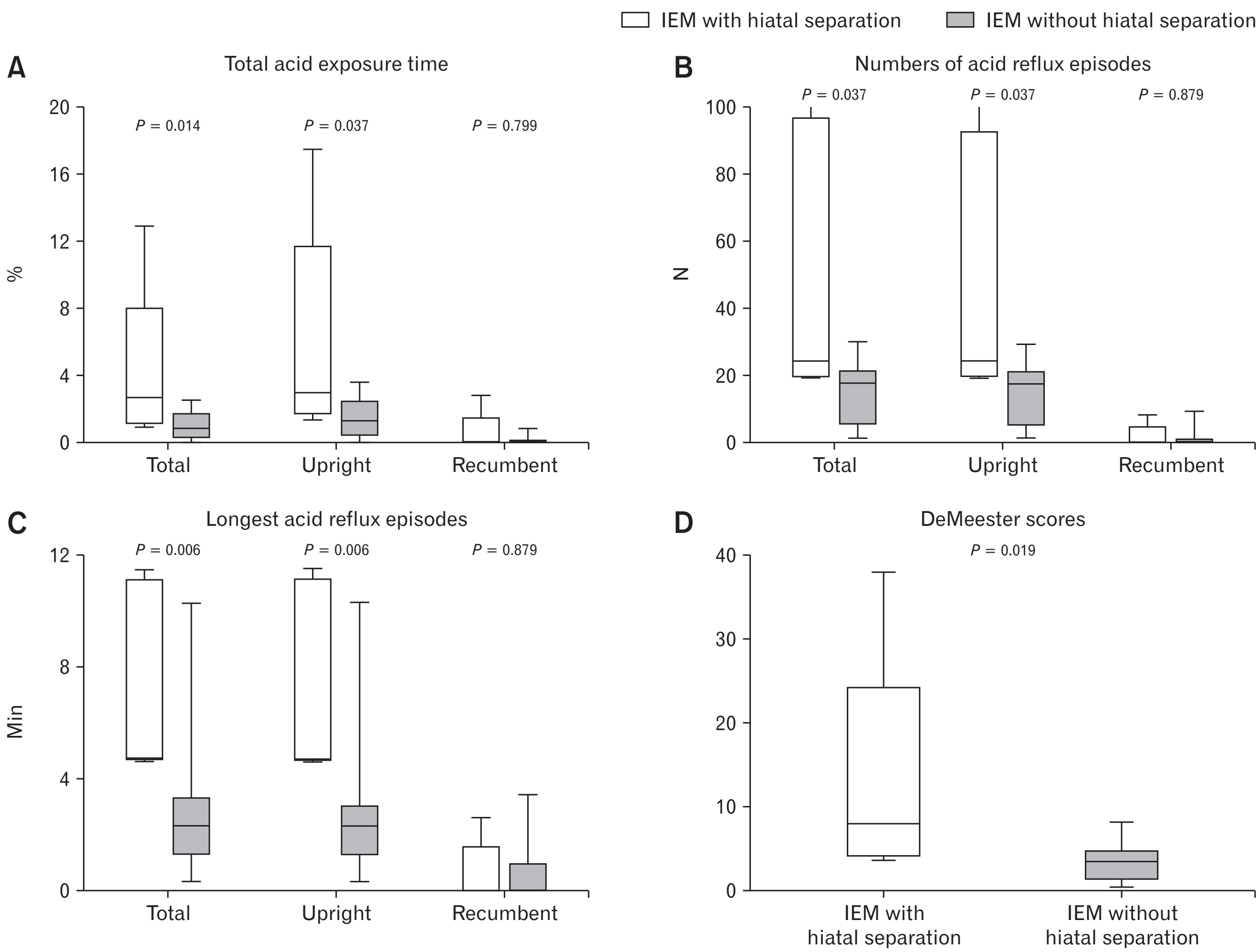

Figure 3. Proportions with (A) total acid exposure time, (B) numbers of acid reflux episodes, (C) longest acid reflux episodes, and (D) DeMeester scores between ineffective esophageal motility (IEM) patients with and without hiatal separation during straight leg raise. IEM with transient hiatal separation (n = 8), IEM without transient hiatal separation (n = 12).

maneuver led to transient hiatal separation, whereas 12 patients did not demonstrate hiatal separation during SLR. Amongst all patient with normal morphology, the presence of transient hiatal separation during SLR did not appear to influence AET, DeMeester score, and longest acid reflux episodes. However, within the IEM patients, median total AET was significantly higher in those patients with transient hiatal separation during SLR ($P = 0.014$; Fig. 3A). Whilst upright AET was also higher ($P = 0.037$) supine AET was not different ($P = 0.799$). Similarly, IEM patients with transient hiatal separation had higher total acid reflux events ($P = 0.037$; Fig. 3B), more frequent longest acid reflux episodes ($P = 0.006$; Fig. 3C), and higher DeMeester scores ($P = 0.019$; Fig. 3D).

Discussion

In this study, we utilized SLR, a novel provocative maneuver during HRM, to examine esophageal function and acid burden in symptomatic GERD patients with normal, transiently abnormal, and consistently abnormal EGJ morphology. We confirmed that structural disruption of the EGJ barrier (presence of a persistent hiatal hernia) can increase AET and reflux events in the distal esophagus. When a transient hiatus hernia was identified during SLR, esophageal acid burden was higher, but only within the subgroup of patients with an IEM diagnosis. To the best of our knowledge, this is the first study to use SLR to provoke hiatal separation in patients who would otherwise have been considered to have normal EGJ morphology based on standard HRM investigation criteria. We conclude that recognition of transient hiatal separation elicited by SLR may have value in clinical evaluation of GERD, particularly within the context of IEM.

Although standard HRM according to the CCv4.0 is currently the gold standard to assess esophageal body motor function and abnormal EGJ relaxation, this has some limitations. Provocative tests can complement and enhance HRM evaluation. Previous studies have shown that abdominal compression can be utilized to challenge the normal esophageal physiology and evaluate EGJ function.[11,12,26,27] Using a tightened belt around the abdomen, an earlier study observed that augmentation of intra-abdominal pressure may induce a hiatus herniation on HRM and increase distal esophageal acid reflux.[28] SLR, a simple maneuver designed to induce an EGJ outflow obstruction-like scenario by increasing intra-abdominal pressure, was recently proposed to assess esophageal contractile reserve and integrity of the EGJ.[13,14] In evaluating the integrity of the EGJ barrier, a recent study demonstrated that although reduction or loss of trans-EGJ gradient between intra-abdominal and intrathoracic cavity during SLR occurs more often in patients with type 3 hiatal hernias, even patients with small hernias or intact EGJ can demonstrate physiological EGJ disruption during SLR.[14] There is evidence to suggest that increasing separation between CD and LES can cause higher reflux burden.[7] In addition to a structurally deficient barrier, EGJ motor abnormalities consist of a hypotensive EGJ and transient LES relaxations, the latter being the most common in GERD. Another study demonstrated that an increase in peak intra-esophageal pressure $\geq$ 100% during SLR was associated with elevated AET in GERD patients, particularly those with type 1 EGJ morphology,[15] suggesting that physiological stress of the EGJ barrier using SLR may predict which patients are most susceptible to reflux events.

IEM, which includes a combination of weak and failed peristalsis with peristaltic breaks, represents the most common among abnormal peristaltic patterns in patients with GERD,[3] with potential reflux implications.[29] In this study, we noted that there were numerical increases in AET and reflux events in IEM patients with transient hiatal separation during SLR. Since the most profound esophageal dysmotility comprises a disrupted EGJ barrier with esophageal body hypomotility,[2] we hypothesized that transient hiatal separation can have higher AET and more reflux events than those without, when the status of esophageal hypomotility is taken into consideration. Our findings demonstrate that this affect is most evident in the subgroup of patients with IEM. More recently, we have demonstrated that application of SLR during HRM can improve esophageal body peristaltic performance and predict esophageal contraction reserve.[13] Our recent work also suggested that measurement of contractile segment impedance during SLR can augment the capability of GERD identification due to the better mucosal contact with impedance sensors.[30] Based on the findings of these studies and our present data, we demonstrate that inclusion of SLR during routine HRM complements evaluation for a disrupted EGJ and GERD, especially in IEM patients with reflux symptoms.

The current study has some notable strengths. This is the first study utilizing SLR to provoke hiatal separation in a GERD population with normal EGJ morphology on standard HRM, and demonstrates the clinical value of including SLR as a provocative test in the routine assessment of GERD patients. Our study utilized a rigorous selection process including complete GERD questionnaires, endoscopic and esophageal functional assessment. Moreover, the present study provides direction on how an intuitive and simple SLR maneuver can identify transient hiatal separation on HRM without computational aid.

There are few limitations that should be mentioned. First, not all patients could complete SLR successfully in our study, particularly patients with poor physical performance, which may have influenced the results. Additionally, the SLR maneuver still lacks standardization, and augmentation of intra-abdominal pressure can be incomplete. Future studies will be required to evaluate if there is intra- or inter-patient variability in SLR responses and to standardize the SLR protocol. Second, we did not compare pH metrics between conclusive and IEM subgroups due to the overall numbers in these subgroups being small, thus limiting further stratification of IEM severity. In addition, we only performed SLR in symptomatic patients with normal EGJ morphology, rather than healthy volunteers for comparison. Evaluation of healthy controls will be needed to acquire normative data and to validate our findings. Third, impedance information was not assessed in this study since some of our HRM studies were performed without impedance. Fourth, we did not assess the intra-esophageal pressure gradient during and before SLR. Evaluation of the relationship between transient hiatal separation and intra-esophageal pressure gradient changes could increase the clinical utility of SLR. Finally, we did not evaluate outcome of patient management in the context of SLR findings, and therefore, it is unknown if SLR findings have direct patient management implications. Further prospective investigations will be needed to determine whether these differences could impact clinical decision making.

In conclusion, the present study demonstrates the value of SLR during HRM as a physiological stress test that may complement evaluation of GERD patients. We show that transient hiatal separation during SLR allows evaluation of physiological disruption of EGJ barrier and can predict acid reflux burden, particularly in IEM patients. Our work supports using this simple maneuver to increase the diagnostic yield in HRM, which may provide adjunctive value in patients with inconclusive evidence of GERD. Further outcome studies are needed to elucidate the clinical relevance of the motor abnormalities revealed by SLR and whether this maneuver can be incorporated into HRM protocols for assessment of EGJ barrier function.

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Conflicts of interest: Taher Omari holds inventorship of the patent family that covers some of the analytical methods described. The Swallow Gateway web application is owned by Flinders University. All other authors report no conflict of interest.

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