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Original Article

Response to multiple rapid swallows shows impaired inhibitory pathways in distal esophageal spasm patients with and without concomitant esophagogastric junction outflow obstruction

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SUMMARY. **Distal esophageal spasm (DES) is a motility disorder characterized by premature contraction of the esophageal body during single swallows. It is thought to be due to impairment of esophageal inhibitory pathways, but studies to support this are limited. The normal response to multiple rapid swallows (MRS) is deglutitive inhibition of the esophageal body during the MRS sequence. Our aim was to compare the response to MRS in DES patients and healthy control subjects. Response to MRS during HRM was evaluated in 19 DES patients (8 with and 11 without concomitant esophagogastric junction outflow obstruction [EGJOO]) and 24 asymptomatic healthy controls. Patients with prior gastroesophageal surgery, peroral endoscopic myotomy, pneumatic dilation, esophageal botulinum toxin injection within 6 months of HRM, opioid medication use, and esophageal stricture were excluded. Response to MRS was evaluated for complete versus impaired inhibition (esophageal body contractility with distal contractile integral [DCI] > 100 mmHg-sec-cm during MRS), presence of post-MRS contraction augmentation (DCI post MRS greater than single swallow mean DCI), and integrated relaxation pressure (IRP). Impaired deglutitive inhibition during MRS was significantly more frequent in DES compared to controls (89% vs. 0%, $P < 0.001$), and frequency was similar for DES with versus without concomitant EGJOO (100% vs. 82%, $P = 0.48$). The proportion of subjects with augmentation post MRS was similar for both groups (37% vs. 38%, $P = 1.00$), but mean DCI post MRS was higher in DES than controls (3360.0 vs. 1238.9, $P = 0.009$). IRP was lower during MRS compared to single swallows in all patients, and IRP during MRS was normal in 5 of 8 patients with DES and EGJOO. Our study suggests that impaired deglutitive inhibition during MRS is present in the majority of patients with DES regardless of whether they have concomitant EGJOO, and future studies should explore the usefulness of incorporating response to MRS in the diagnosis of DES.**

KEY WORDS: **distal esophageal spasm, high-resolution esophageal manometry, multiple rapid swallows.**

INTRODUCTION

Distal esophageal spasm (DES) is a motility disorder characterized by premature contraction of the esophageal body during single swallows, usually presenting with dysphagia and chest pain.[1,2] DES is not a common condition, found in less than 5% of patients undergoing esophageal motility testing for dysphagia.[3] In 1958, DES was described manometrically by Creamer et al. as a replacement of peristaltic waves by a simultaneous and prolonged rise of pressure in the distal esophagus.[4,5] For a long time, based on conventional, low-resolution manometry and line tracings, DES was defined by the presence of simultaneous esophageal contractions in >10% of wet swallows, with intermittent normal peristalsis.[1,2] In 2011, using high-resolution esophageal manometry (HRM) and esophageal pressure topography analysis, Pandolfino et al. found that compared to velocity of contractile front, reduced distal latency (DL) correlates better with esophageal symptoms.[6] More recently, the most current version of the Chicago classification of esophageal motor disorders based on HRM (version 3.0) defined DES as the presence of reduced DL (≤4.5 seconds) in ≥20% swallows.[7] Some

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patients with DES may have concomitant esophagogastric junction outflow obstruction (EGJOO) defined by a median integrated relaxation pressure >15 mmHg, but they do not meet criteria for achalasia type III because peristalsis is normal in some swallows and spastic in others (there is no normal peristalsis in achalasia type III).

Although the pathophysiology of DES is not completely understood, it is thought to be due to impairment of esophageal inhibitory pathways, resulting in premature contractions in the distal esophagus, but studies to support this are limited.[8] In contrast, in healthy individuals, a balance between excitatory and inhibitory stimuli plays an important role in the organized and sequential esophageal body contractility seen during normal esophageal peristalsis.[9–11] Quickly after deglutition, a normal wave of inhibition to the esophageal muscle, called deglutitive inhibition, spreads over to the entire distal esophageal body, lasting longer in progressively more distal segments.[9,11] Some authors have validated that afferent signals starting from the pharynx inhibit progression of primary esophageal peristalsis, regardless of the amount of volume ingested.[12–14] This inhibition is followed by excitation, which is induced by lumen distension in order to maintain esophageal clearance of residual food bolus after swallowing.[14–17]

Assessment of response to multiple rapid swallows (MRS) during HRM enables detection of impaired inhibition during MRS. Of note, impaired inhibition may also lead to incomplete EGJ relaxation, manifested manometrically as EGJOO. Healthy subjects respond to MRS by deglutitive inhibition during the MRS sequence, followed by a post-MRS peristaltic contraction that often has increased contractile vigor compared to that of single swallows. We hypothesized that deglutitive inhibition is impaired in DES patients. Our aim was to compare response to MRS in DES patients (with and without concomitant EGJOO) and asymptomatic healthy control subjects.

MATERIALS AND METHODS

Subjects

Patients diagnosed with DES based upon Chicago classification v3.0 were identified from a prospectively maintained esophageal motility database at Mayo Clinic, Scottsdale, Arizona, USA. HRM was performed after informed consent in asymptomatic healthy control subjects at Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico. Demographic data and symptom presentation in DES patients was obtained from the motility database as well as medical chart review and collected prospectively in the control subjects. Patients with prior gastroesophageal surgery, pneumatic dilation, peroral endoscopic myotomy (POEM), esophageal botulinum toxin injection within 6 months of HRM, opioid medication use, and esophageal stricture were excluded. The Institutional Review Board (IRB) approved the study.

High-resolution esophageal manometry (HRM)

HRM was performed following the same testing protocol in all study subjects (DES patients and healthy controls), using a catheter with 36 circumferential solid-state pressure sensors spaced at 1-cm intervals (Medtronic). Ten 5-ml liquid single swallows were administered, followed by an MRS sequence which consisted of five 2-ml rapid sequence liquid swallows.

Analysis of HRM was completed using ManoView software (Medtronic, Duluth, GA). Esophagogastric junction (EGJ) resting pressure, EGJ integrated relaxation pressure (IRP), DL, and distal contractile integral (DCI) were calculated for the 10 single swallows, and Chicago classification v3.0 was applied to diagnose esophageal motility disorders.[18] DES was defined by the presence of ≥20% swallows with DL ≤ 4.5 seconds and normal median IRP. Patients with elevated median IRP (>15 mmHg) and ≥20% swallows with DL ≤ 4.5 seconds, but who had some preserved normal peristalsis and thus did not meet criteria for achalasia type III, were considered as having DES with concomitant EJGOO. Two parameters were used to assess the esophageal body contractile response to MRS: (a) complete versus impaired inhibition (the latter defined as esophageal body contractility with DCI > 100 mmHg-sec-cm during MRS) and (b) presence of post-MRS contraction augmentation, defined as DCI post MRS greater than single swallow mean DCI.[18] Integrated relaxation pressure (IRP) was also measured during MRS. Any study that did not follow protocol or contained artifact was excluded.

Power analysis

The primary goal of the proposed study was to test the null hypothesis that the proportion of subjects with impaired inhibition during MRS would be identical between patients with DES and asymptomatic controls. The criterion for significance (alpha) was set at 0.05 (two-tailed). A sample size of 18 subjects in each of the two groups (total $n = 36$), has greater than 80% power to yield a statistically significant result using the assumption that the difference in proportions is 0.5 (controls = 30% vs. DES = 80%). This effect was selected as the smallest effect that would be important to detect, in the sense that any smaller effect would not be of clinical or substantive significance.[19]

Table 1 Demographic data and symptoms

	DES ($n = 19$)	Healthy controls ($n = 24$)	P-value
Age mean (SD) (years)	63.79 (11.19)	34.04 (7.79)	<0.001
Female n, (%)	11 (58)	14 (58)	1.00
BMI mean (SD) (kg/m^2)	29.99 (8.23)	24.41 (4.14)	0.014
Symptoms, n (%)			
Dysphagia	8 (42)	0	
Chest pain	3 (16)	0	
GERD symptoms	6 (32)	0	
Other symptoms	2 (10)	0	
Asymptomatic	0	24 (100)	

DES, distal esophageal spasm; BMI, body mass index; GERD, gastroesophageal reflux disease

Table 2 Mean values for standard high-resolution manometry metrics among patients with distal esophageal spasm and asymptomatic healthy controls

	DES ($n = 19$)	Healthy controls ($n = 24$)	P-value
EGJ resting pressure	29.56 (20.33)	20.13 (9.75)	0.163
IRP	13.46 (9.79)	7.30 (4.90)	0.028
DCI	3169.80 (1609.52)	1295.13 (1030.95)	<0.001
DL	4.25 (0.62)	6.83 (1.54)	<0.001

DES, distal esophageal spasm; EGJ, esophagogastric junction; IRP, integrated relaxation pressure; DCI, distal contractile integral; DL, distal latency. Values are presented as mean (SD)

Statistical analysis

Continuous data are presented as means with standard deviations (SD). Categorical data are summarized as frequencies and percentages. Data was assessed using graphical and descriptive functions to evaluate the distributions and assess for outliers. The differences between continuous variables were assessed using Student t-tests and ANOVA. Fisher's exact tests were used to assess distributions for categorical variables. Results were considered statistically significant at a (two-tailed) P-value of <0.05. All statistical analyses were completed using JMP®, Version 14.2 (SAS Institute Inc., Cary, NC).

RESULTS

Demographic data and symptoms

The study included 19 patients with DES (8 with and 11 without concomitant EGJOO) and 24 asymptomatic healthy control subjects. Demographic and symptom data is shown in Table 1. DES patients were older and had higher BMI compared to controls; 89.5% were Caucasian and 10.5% were Hispanic, whereas 100% of controls were Hispanic; there were no differences in gender. The most frequent symptoms in DES patients were dysphagia, GERD symptoms, and chest pain.

Standard HRM metrics

Standard Chicago classification metrics derived from the 10-swallow study are shown in Table 2. Compared to controls, DES patients had a higher mean IRP (13.46 mmHg vs. 7.30 mmHg, $P = 0.028$), higher mean DCI (3169.80 vs. 1295.13, $P < 0.001$), and lower mean DL (4.25 vs. 6.83, $P < 0.001$). The mean EGJ resting pressure was not statistically different among the two groups ($P = 0.16$). As expected, mean IRP was higher in patients with DES + EGJOO compared to those with DES alone (25.09 mmHg vs. 7.46 mmHg, $P < 0.001$); mean DL was similar for DES patients with versus without EGJOO (4.26 vs. 4.23, $P = 0.93$). Mean IRP was similar among DES patient without EGJOO and controls (7.46 mmHg vs. 7.30 mmHg, $P = 0.92$).

Response to multiple rapid swallows

Examples of normal and impaired inhibition during MRS are presented in Figure 1. Impaired inhibition of esophageal body contractility during MRS was significantly more frequent in DES patients compared to healthy controls (89% vs. 0%, $P < 0.001$). Impaired deglutitive inhibition was very frequent in DES patients both with versus without concomitant EGJOO (100% and 82%, respectively, $P = 0.48$), and it was significantly more frequent in DES patients without EGJOO compared to controls (82% vs. 0%, $P < 0.001$).

The vigor of esophageal body contractility measured by mean DCI during the MRS sequence was significantly higher in DES patients compared to controls (1202.79 vs. 12.60 mmHg-cm-s, $P < 0.001$). The proportion of subjects with augmentation post MRS was similar for DES and controls (37% vs.

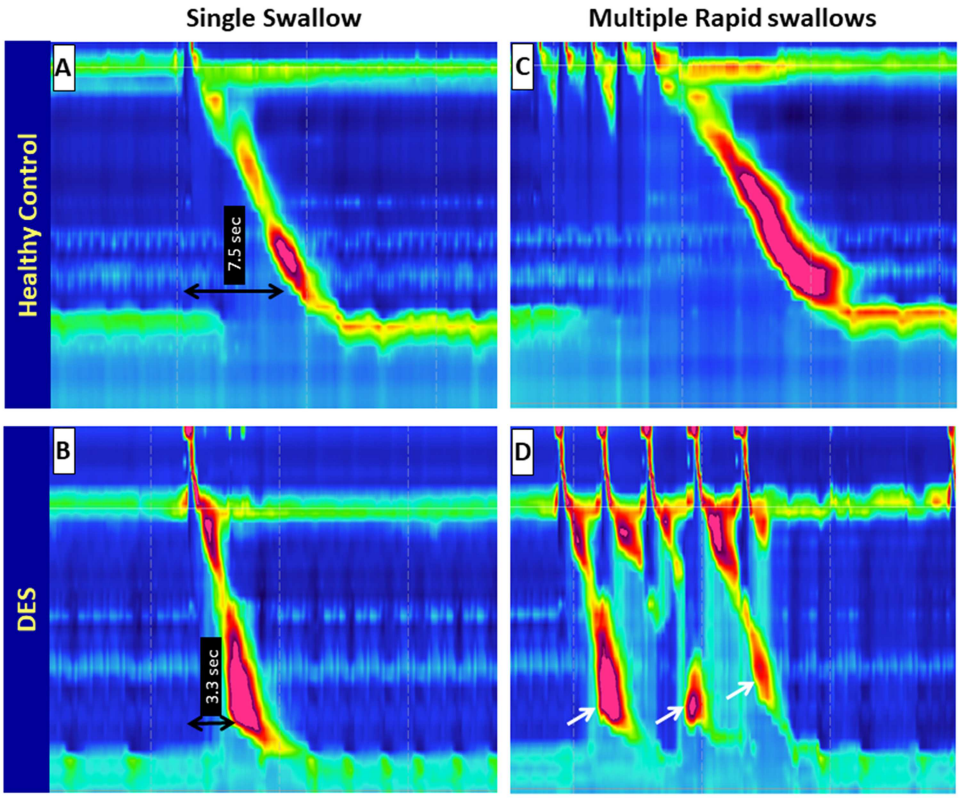

Fig. 1 Response to a single swallow and multiple rapid swallows (MRS) in a healthy control subject and a patient with distal esophageal spasm (DES). (A) Normal distal latency of 7.5 seconds after a single swallow in a healthy control. (B) Premature contractility after a single swallow in a DES patient, with reduced distal latency of 3.3 seconds. (C) Normal deglutitive inhibition in a healthy control, with absence of esophageal body contractility during MRS. (D) Impaired deglutitive inhibition in a DES patient, with esophageal body contractility (white arrows) during MRS.

38%, $P = 1.00$). However, post-MRS peristaltic contraction mean DCI was significantly higher in DES patients compared to controls (3360.0 vs. 1238.93 mmHg-cm-s, $P = 0.009$).

Mean IRP during MRS was higher in patients with DES + EGJOO compared to DES patients without EGJOO and healthy subjects (14.6 vs. 1.4 vs. 3.1 mmHg, $P < 0.001$). IRP during MRS was similar for patients with DES without EGJOO and healthy subjects (1.4 vs. 3.1 mmHg, $P = 0.701$). Of note, IRP during MRS was lower than median single swallow IRP in all the DES patients included in the study. The difference between mean IRP during MRS and single swallows was −6.82 mmHg, −10.53 mmHg, and −4.19 mmHg for DES, DES + EGJOO, and controls group, respectively ($P = 0.029$), as shown in Figure 2. Furthermore, based upon a threshold of 15 mmHg, IRP normalized in five of the eight patients with DES and concomitant EGJOO.

DISCUSSION

Primary peristalsis is characterized by a sequence of esophageal contractions that proceed aborally in an orderly fashion, requiring a latency that increases gradually from proximal to distal esophagus. This increasing latency is determined by the pattern of activation and regional gradients of inhibitory and excitatory signals in the esophagus.[9–11,15,20] DES is characterized by premature contraction of the esophageal body during single swallows. While the pathophysiology of DES has not been fully elucidated, this esophageal motor disorder is thought to be due to impaired inhibitory signaling in the esophagus, leading to reduced latency and premature contractions.[13] Using conventional low-resolution manometry combined with an intraesophageal balloon, Sifrim et al. showed impaired deglutitive inhibition in 6 patients with DES.[11]

Response to MRS is a provocative maneuver that can be performed during HRM to assess the integrity of deglutitive inhibition.[21–24] The normal response to multiple swallows taken in rapid succession is for the esophageal body to remain inhibited until the last of the series of swallows, after which there is a peristaltic contraction, often with higher contractile vigor than what is seen following a single swallow.[21,24] This normal response to MRS requires intact inhibitory signaling pathways. Somewhat similar to MRS, the rapid drink challenge (RDC) entails rapid swallowing of 200 mL of water and is another provocative maneuver that can be performed during HRM to assess deglutitive inhibition.[25,26] In a study that included 17 patients with DES and jackhammer esophagus (unclear as to how many of each), response to RDC showed

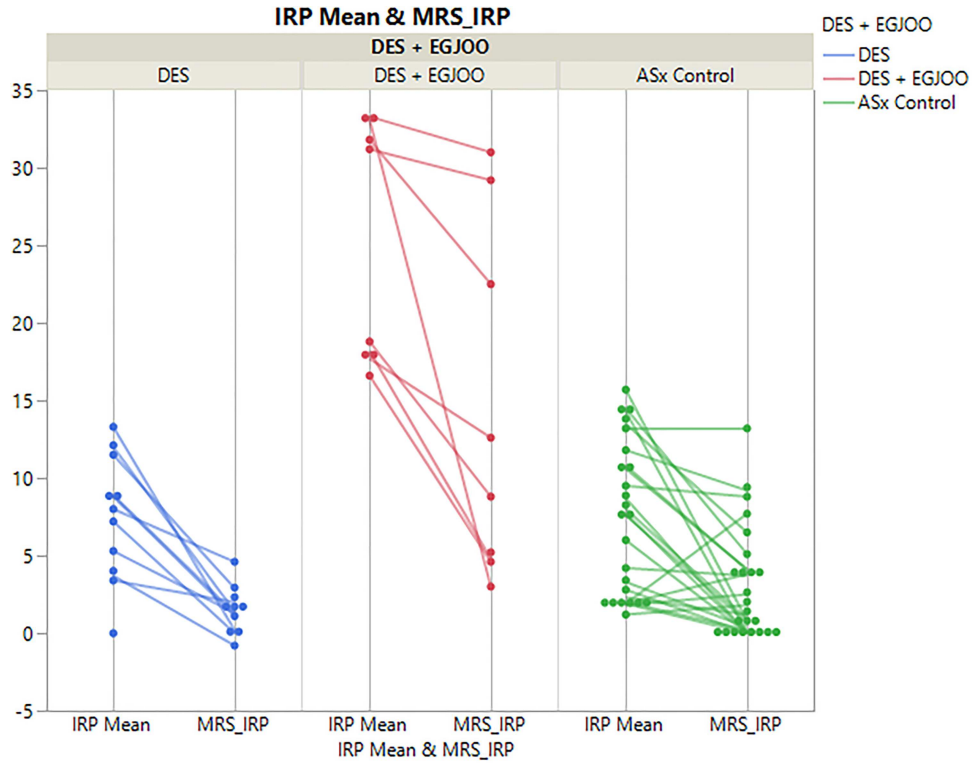

Fig. 2 Difference between mean IRP during single swallows (SS) and multiple rapid swallows (MRS) among patients with distal esophageal spasm (DES) only, distal esophageal spasm and concomitant esophagogastric outflow obstruction (DES + EGJOO), and asymptomatic controls (Asx Control).

impaired deglutitive inhibition in 65% of them.[25] In our study which was based on MRS rather than RDC, impaired deglutitive inhibition in DES patients was more frequent. This could mean that MRS may be better at detecting impaired inhibition, but the difference could also be due to the fact that we focused only on DES patients, instead of including both DES and jackhammer. An interesting finding in the present study was that IRP for all DES patients was lower during MRS compared to the IRP seen during single swallows, which is in keeping with other studies that have found more profound EGJ relaxation during MRS. In fact, the IRP normalized in several patients with DES and concomitant EGJOO. This suggests that the impaired inhibition in the EGJ can be partially circumvented by the MRS sequence, but our numbers are too small to glean the clinical significance of this. Also, this 'normalization' of the IRP is based on the 15 mmHg threshold used during single swallows, and normal values for IRP during MRS are not well established.

While others have shown impaired deglutitive inhibition during MRS using conventional manometry, to our knowledge our study is the first one to assess response to MRS during HRM in DES patients. We found that impaired inhibition during MRS was never seen in healthy controls, but it is extremely frequent in DES patients, regardless of whether there is concomitant EGJOO. Furthermore and as expected, DCI measured during the MRS sequence was significantly higher in the DES group. Our findings provide additional and strong support for impaired inhibitory signaling as a pathophysiological mechanism in DES patients. Response to MRS during HRM has recently been used to show altered inhibitory function in patients with jackhammer esophagus with and without EGJOO.[27] Similarly, we have recently used this approach to document impaired inhibitory pathways in patients with opioid-induced esophageal dysmotility.[28] Of note, we excluded patients on opioids from our current study, as we felt it was important to avoid including patients with opioid-induced impaired inhibition.

In terms of the practical and clinical relevance of our findings, it is important to note that the diagnosis of DES can at times be challenging. The contractile deceleration point that is used to measure distal latency and diagnose DES is at times difficult to pinpoint, and minor adjustments to this measurement can lead to diagnosing or excluding DES. Therefore, we suggest that impaired deglutitive inhibition during MRS should be considered as an adjunct measure that can be used to make a diagnosis of DES. This may be especially useful in those patients in whom the diagnosis of DES is inconclusive, equivocal, or borderline. Of course, additional studies will be needed to clarify whether adding impaired deglutitive inhibition to the

diagnostic criteria results in better correlation with symptoms, along with an improved ability to predict the need for and response to therapy.

The present study has some limitations. Firstly, the sample size is relatively small. However, we anticipated big differences among the groups in the power analysis, and the striking disparity in the frequency of abnormal response to MRS in DES versus healthy controls allowed us to find highly significant differences even with a modest number of subjects in each group. Secondly, we assessed response to a single MRS sequence, and a recent study suggested that three MRS sequences are needed for accurate prediction of contraction reserve (defined by contractile vigor of post-MRS peristalsis).[29] While IRP measurement during MRS has been found to be reliable with a single MRS sequence,[30] the optimal number of MRS sequences needed to accurately assess impaired esophageal body contractile inhibition has not been defined. Lastly, different age group and ethnicity among DES patients and healthy controls should be considered; of note Vega et al. previously showed that there were no differences in LES pressure and distal esophageal body function among Hispanic and Caucasian American healthy volunteers.[31]

In conclusion, impaired deglutitive inhibition during MRS is present in the majority of patients with DES, supporting impaired inhibitory pathways in the esophagus as a mechanism of action in this disorder. Impaired inhibition during MRS could potentially be incorporated as part of the diagnostic criteria for DES, especially in patients in whom the diagnosis of DES may be inconclusive, but additional studies will be needed to determine whether this may result in better correlation with esophageal symptoms or improvements in the ability to predict response to therapy.

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