Am J Physiol Gastrointest Liver Physiol 316: G397–G403, 2019.
First published December 13, 2018; doi:10.1152/ajpgi.00342.2018.

RESEARCH ARTICLE | *Neurogastroenterology and Motility*

Provocative testing in patients with jackhammer esophagus: evidence for altered neural control

Aurelio Mauro,[1,2] Farhan Quader,[3] Salvatore Tolone,[4] Edoardo Savarino,[5] Nicola De Bortoli,[6] Marianna Franchina,[1,2] C. Prakash Gyawali,[3] and Roberto Penagini[1,2]

[1]*Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy;* [2]*Gastroenterology and Endoscopy Unit, Fondazione IRCCS Cà Granda, Ospedale Maggiore Policlinico, Milan, Italy;* [3]*Division of Gastroenterology, Washington University School of Medicine, St. Louis, Missouri;* [4]*Division of General and Bariatric Surgery, Department of Surgery, Second University of Naples, Naples, Italy;* [5]*Division of Gastroenterology, Department of Surgery, Oncology and Gastroenterology, University of Padua, Padua, Italy; and* [6]*Division of Gastroenterology, Department of Translational Research and New Technology in Medicine and Surgery, University of Pisa, Cisanello Hospital, Pisa, Italy*

Submitted 12 October 2018; accepted in final form 10 December 2018

Mauro A, Quader F, Tolone S, Savarino E, De Bortoli N, Franchina M, Gyawali CP, Penagini R. Provocative testing in patients with jackhammer esophagus: evidence for altered neural control. *Am J Physiol Gastrointest Liver Physiol* 316: G397–G403, 2019. First published December 13, 2018; doi:10.1152/ajpgi.00342.2018.—Jackhammer esophagus (JE) is a hypercontractile disorder, the pathogenesis of which is incompletely understood. Multiple rapid swallows (MRS) and rapid drink challenge (RDC) are complementary tests used during high-resolution manometry (HRM) that evaluate inhibitory and excitatory neuromuscular function and latent obstruction, respectively. Our aim was to evaluate esophageal pathophysiology using MRS and RDC in 83 JE patients (28 men; median age: 63 yr; IQR: 54–70 yr). Twenty-one healthy subjects (11 men; median age: 28 yr; range: 26–30 yr) were used as a control group. All patients underwent solid-state HRM with ten 5-ml single swallows (SS) and one to three 10-ml MRS; 34 patients also underwent RDC. Data are shown as median (interquartile range). Abnormal motor inhibition was noted during at least one MRS test in 48% of JE patients compared with 29% of controls ($P = 0.29$). Mean distal contractile integral (DCI) after MRS was significantly lower than after SS [6,028 (3,678–9,267) mmHg·cm·s vs. 7,514 (6,238–9,197) mmHg·cm·s, $P = 0.02$], as was highest DCI ($P < 0.0001$). Consequently, 66% of JE patients had no contraction reserve. At least one variable of obstruction during RDC (performed in 34 patients) was outside the normal range in 25 (74%) of JE patients. Both highest DCI after SS and pressure gradient across the esophagogastric junction (EGJ) during RDC were higher in patients with dysphagia versus those without ($P = 0.04$ and 0.01, respectively). Our data suggest altered neural control in JE patients with heterogeneity in inhibitory function. Furthermore, some patients had latent EGJ obstruction during RDC, which correlated with the presence of dysphagia.

NEW & NOTEWORTHY Presence of abnormal inhibition was observed during multiple rapid swallows (MRS) in some but not all patients with jackhammer esophagus (JE). Unlike healthy subjects, JE patients were more strongly stimulated after single swallows than after MRS. An obstructive pattern was frequently observed during rapid drink challenge (RDC) and was related to presence of dysphagia. MRS and RDC during high-resolution manometry are useful to show individual pathophysiological patterns in JE and may guide optimal therapeutic strategies.

Address for reprint requests and other correspondence: A. Mauro, Via Francesco Sforza 35, 20122 Milan, Italy (e-mail: aurelio.mauro@unimi.it).

dysphagia; high-resolution manometry; jackhammer esophagus; multiple rapid swallows; rapid drink challenge

INTRODUCTION

Jackhammer esophagus (JE) is a hypercontractile motility disorder characterized by the presence of vigorous peristaltic waves that may be associated with dysphagia and/or chest pain (30). With conventional manometry, a hypercontractile motor pattern characterized by the presence of high amplitude (>180 mmHg) peristaltic waves in the distal esophagus was termed "nutcracker esophagus" (33). The development of esophageal high-resolution manometry (HRM) has allowed detailed spatial definition of motor activity in the entire esophagus (9). With HRM, a new metric was introduced and used to assess vigor of esophageal smooth muscle contractility: the distal contractile integral (DCI). This takes into account the amplitude, duration, and length of the contractile segment (25), therefore allowing accurate characterization of smooth muscle contractile activity in the distal esophagus. The latest version of the Chicago Classification of motor disorders defines JE as the presence of more than 20% of swallows with a DCI > 8,000 mmHg·cm·s (17) based on available data and consensus opinion suggesting that this degree of hypercontractility is not encountered in healthy asymptomatic individuals.

The pathophysiology of JE is incompletely understood. The prevailing hypothesis suggests that exaggerated smooth muscle contraction results from an excess of cholinergic drive that leads to excessive excitation or myocyte hypertrophy (11, 18). The associations between JE on the one hand and gastroesophageal reflux disease and obstruction of esophagogastric junction (EGJ) on the other remain incompletely understood (1, 7). Impaired deglutitive inhibition has been reported in distal esophageal spasm (4) and nutcracker esophagus (32). Because imbalance between excitatory and inhibitory forces in the smooth muscle esophagus has been proposed as a mechanism for exaggerated contraction, provocative testing evaluating esophageal physiology could add to our understanding of JE (15, 16). Multiple rapid swallows (MRS) is a provocative test performed during HRM that assesses both deglutitive inhibition and subsequent smooth muscle contraction (13, 31, 34),

whereas rapid drink challenge (RDC) assesses deglutitive inhibition and evaluates for latent EGJ obstruction (2, 20). Physiologically, both MRS and RDC provoke an intense central and peripheral neural inhibition, resulting in absence of contraction in the smooth muscle portion of the esophagus along with prolonged and complete relaxation of the lower esophageal sphincter (LES). The last swallow of the MRS series is followed by a powerful peristaltic sequence in the esophageal body, with a postrelaxation contraction in the LES RDC does not always elicit a postrelaxation contraction. Thus, a normal response to MRS requires integrity of inhibitory mechanisms and the capacity of esophageal muscle to respond to a strong stimulation at the end of the MRS (13). The ability to augment peristaltic performance following MRS is also called contraction reserve (31, 34). Using conventional manometry, motor inhibition was identified in nutcracker esophagus using 5-ml swallows at varying time intervals ranging from 5 to 30 s apart (6); in contrast, motor inhibition was found to be diminished in nutcracker patients with multiple peaked waves (similar to that seen in distal esophageal spasm) using standard swallows and a sophisticated balloon sensor to measure inhibition (32). However, responses to the standardized MRS test (swallows of 2 ml of water at intervals of 2–3 s for a total of 10 ml of water) have not been reported, and only limited data exist regarding RDC responses in JE patients (2, 21).

The primary aim of this observational cohort study was to evaluate esophageal deglutitive inhibition and post-MRS contraction using standardized provocative testing in JE patients in comparison to that observed in healthy asymptomatic controls. Secondary aims were to better define esophageal physiology, pathophysiology, and EGJ obstruction using RDC and determine relationships to symptomatic presentation in JE patients.

METHODS

Adult patients referred for HRM at four Italian and one American tertiary centers (Milan, Padua, Pisa, Naples, and St. Louis, MO) between February 2016 and September 2017 were considered for this observational cohort study. The primary inclusion criterion was a manometric diagnosis of JE according to Chicago Classification v. 3.0 (at least 20% sequences with DCI $>$ 8,000 mmHg·cm·s) (17). In addition to a standard 10-swallow HRM protocol of 5 ml water in the supine position, inclusion required at least one MRS sequence; RDC was not a requirement for study inclusion. Exclusion criteria consisted of esophageal outflow obstruction on HRM [integrated relaxation pressure (IRP) $>$ 15 mmHg), eosinophilic esophagitis, known obstructive esophageal disorders, prior esophageal or gastric surgery, incomplete HRM studies, and lack of at least one MRS sequence during the HRM protocol. The presence and nature of presenting symptoms were assessed by retrospectively reviewing the standardized medical interview and/or patient questionnaires, specifically assessing for presence or absence of reflux symptoms, dysphagia, and chest pain during patient evaluation (14, 28). HRM studies from 21 healthy subjects (median age, 28 yr; range, 26–30 yr; 10 women) using a similar HRM protocol [single swallows (SS), MRS] were utilized as comparative normative control data (31). This study protocol involving review of HRM studies and related patient data was approved by the respective institutional review boards at all study centers.

Esophageal High-Resolution Manometry

HRM was performed using a 4-mm solid-state probe with 36 circumferential sensors at 1-cm intervals (Medtronic, Minneapolis, MN), using previously published methodology (23, 27). Manometric pressure data were visualized as topographic contour plots (Clouse plots) on a dedicated screen and were stored for subsequent analysis using ManoView software (Medtronic). In all cases, the esophageal manometry catheter was passed transnasally under topical anesthesia (lidocaine spray or gel) after an overnight fast and positioned with the tip in the stomach. Patients were placed in the recumbent position and were asked to refrain from swallowing during 30 s of baseline recording of LES tone. Following this, the manometry protocol consisted of ten 5-ml SS of water at intervals of 20–30 s and one to three MRS (i.e., swallows of 2 ml of water administered using a syringe at intervals of 2–3 s, while the operator monitored the rhythm of swallows, for a total of 10 ml of water) (23, 27). Finally, whenever possible, patients were asked to drink 100–200 ml of water as quickly as possible (RDC) in the sitting position.

Data Analysis

Single swallows. HRM studies were analyzed to extract standard HRM metrics [IRP, DCI, distal latency (DL)] utilized in the Chicago Classification v. 3.0 using established methodology (17). The number of hypercontractile waves with DCI $>$ 8,000 mmHg·cm·s, mean DCI, and highest DCI values were extracted from the HRM studies. Contractile front velocity (CFV) and DL of hypercontractile waves were compared with values obtained from nonhypercontractile effective sequences (DCI $<$ 8,000 mmHg·cm·s and $>$ 450 mmHg·cm·s).

Multiple rapid swallows and rapid drink challenge. During MRS, the 4-s IRP and motor inhibition (absence of motor activity of $>$3 cm length using a 30-mmHg isobaric contour in the esophageal body) (12) were evaluated. Pressurizations and contraction of striated proximal section of the esophagus were not included for the evaluation of motor inhibition. In patients with contraction during expected motor inhibition during MRS, a contractile integral was calculated using a 20-mmHg isobaric contour with the DCI tool.

After MRS, the number of hypercontractile waves, mean, and highest values of DCI were evaluated and compared with those obtained during SS. CFV and DL of hypercontractile waves were compared with values obtained with the normal waves. Contraction reserve was calculated as the ratio between the mean MRS DCI and the mean SS DCI.

When RDC was performed, the ratio between the post-RDC DCI (when present) and the mean SS DCI of SS was evaluated. To evaluate for EGJ obstruction, the number of panesophageal pressurizations above 20 mmHg, duration of these pressurizations (as a percentage of duration of RDC), mean IRP, and gradient across the EGJ were measured according to methodology described by Marin et al. (20). Specifically, the trans-EGJ gradient was measured using software tools with mean (intrabolus) pressure measured 2 cm above and below the EGJ across the entire duration of RDC, and the gradient was calculated in mmHg as the difference of the two values.

Symptoms. Hypercontractile variables (mean and highest DCI during SS and MRS), RDC variables (number of pressurization, pressurization time, and gradient across EGJ), and percentage of patients without motor inhibition or contraction reserve (MRS) were compared between symptomatic (i.e., dysphagia and chest pain) and asymptomatic patients. Data from patients undergoing 100- and 200-ml RDC were merged for symptom analysis.

Statistical Analysis

Data are described as median values with interquartile ranges (IQRs) unless otherwise reported. The Wilcoxon rank sum test was used to compare HRM variables between SS, MRS, or RDC within the JE cohort. Mann-Whitney or χ^2-test was used as appropriate to compare data between the JE cohort and asymptomatic controls (8 men; 28 yr; 26–30) (31) and between symptomatic and asymptomatic JE patients. Statistical analyses were performed using SPSS (version

Table 1. *High-resolution manometry variables during single and multiple rapid swallows in jackhammer esophagus patients and healthy controls*

	JE Patients	Healthy Controls
Single swallows		
4-s IRP, mmHg	8.1 (8.4); 0–20.8*	5.9 (5.9); 1.2–13.7‡
IBP, mmHg	14 (10.6); 1–40†	11.2 (7.7); 2.5–18.6‡
DL, s	6.7 (1.3); 4.7–10†	7.6 (1.4); 5.5–9.9
CFV, cm/s	3.4 (1.8); 1.7–12*	3.3 (0.9); 2.1–5.1§
Multiple rapid swallows		
4-s IRP, mmHg	5.5 (6.3); −0.6 to 24.5	2.2 (4); 0–13.2
IBP, mmHg	16.5 (12); 1–40	13 (4.3); 6.8–17.4
DL, s	6.4 (2); 1.2–14.1	8.4 (2.8); 3.5–11
CFV, cm/s	4.2 (3.3); 1.3–22	2.7 (1.1); 2–4.6

Values are medians (interquartile ranges); full ranges. CFV, contraction front velocity; DL, distal latency; IBP, intrabolus pressure; IRP, integrated relaxation pressure; JE, jackhammer esophagus; MRS, multiple rapid swallows. *$P < 0.005$ vs. JE MRS; †$P < 0.05$ vs. JE MRS; ‡$P < 0.01$ vs. healthy controls MRS; §$P = 0.01$ vs. healthy controls MRS.

21, IBM, Armonk, NY). In all instances, a P value of <0.05 was required for statistical significance.

RESULTS

Over the study period, 83 patients with JE (28 men; median age: 63 yr; IQR: 54–70 yr) fulfilled inclusion criteria for this study. Dysphagia and chest pain were the predominant presenting symptoms (59 and 52% of patients, respectively); heartburn or acid regurgitation was reported by 45%. Upper gastrointestinal endoscopy, performed in all patients, was normal in the majority (58%); spastic contractions were reported in 10%, whereas hiatal hernia was found in 27%. Esophagitis was rare, reported in only 5%. X-ray barium swallow was performed in 28 patients, showing tertiary contractions in three, hiatal hernia in three, and normal findings in the remaining 22 patients.

Descriptive HRM parameters during SS and MRS in JE patients and asymptomatic controls are detailed in Table 1. When normal sequences were compared with hypercontractile sequences with SS, neither CFV [mean, 3.5 (IQR, 2.9–4.7) vs. 3.3 (2.7–4.2) cm/s, respectively; $P = 0.07$] nor DL [6.6 (6–7.6) vs. 6.9 (6.2–7.8) s, respectively; $P = 0.23$] were different.

Inhibitory Activity During Multiple Rapid Swallows

The majority of JE patients ($n = 56$, 68%) performed two MRS sequences, 14 patients (17%) performed three, and 13 (16%) performed one. Nineteen of the 21 asymptomatic controls performed two MRS sequences, and the remainder performed one.

As expected, 4-s IRP was significantly lower during MRS than SS in both JE patients and asymptomatic controls (Table 1). However, 4-s IRP values following MRS reached a lower nadir in asymptomatic controls compared with JE patients ($P = 0.01$); values were statistically similar during SS in both groups ($P = 0.12$). Abnormal motor inhibition was noted in at least one MRS sequence in 40 JE patients (48%) and in all available MRS sequences in 19 JE patients (23%); these were not significantly different from asymptomatic controls (24 and 15%, respectively; $P = 0.10$). In JE patients, median contractile integral of motor activity during MRS was 718 mmHg·cm·s (391–1,460 mmHg·cm·s); 44 of 64 MRS without motor inhibition (69%) had a contractile integral of motor activity > 450 mmHg·cm·s, whereas in asymptomatic controls only 3 of 8 MRS without motor inhibition (38%) had a similar contractile integral ($P = 0.08$ vs. JE), suggesting a greater (although not statistically significant) impact of absence of motor inhibition in JE patients. An example of absence of motor inhibition during MRS in JE is shown in Fig. 1.

Contractile Activity After MRS

Interestingly, hypercontractile activity was less evident after MRS than after SS in JE patients: proportions of hypercontractile sequences were lower following MRS than with SS (34 vs. 45%; $P = 0.01$). Mean DCI after MRS was significantly lower than with SS [6,028 (3,678–9,267) mmHg·cm·s vs. 7,514 (6,238–9,197) mmHg·cm·s; $P = 0.02$]. This difference was more pronounced when the highest DCI values during MRS and SS were compared [8,884 (4,585–11,741) mmHg·cm·s vs. 9,775 (9,178–12,259) mmHg·cm·s; $P < 0.0001$] (Fig. 2*A*). Furthermore, when contraction reserve was analyzed, 55 of 83

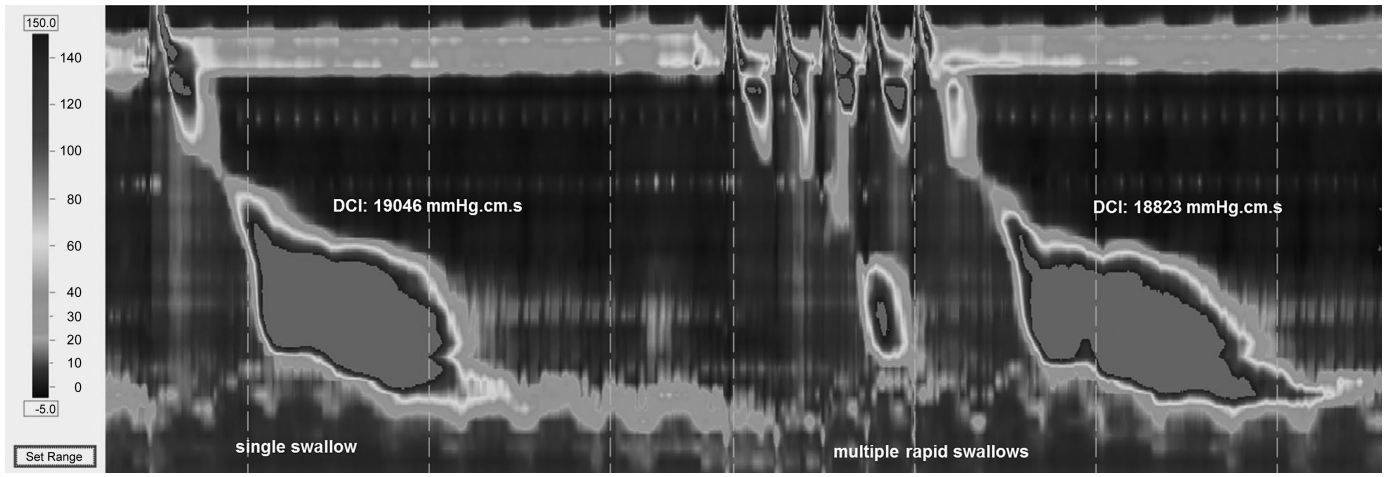

Fig. 1. Single swallows (SS) and multiple rapid swallows (MRS) from a patient with jackhammer esophagus (JE). There is a short segment of contraction during MRS, indicating abnormal inhibition. Furthermore, esophageal smooth muscle is maximally stimulated during SS, and there is no further reserve for augmentation of contraction following MRS. These findings demonstrate an imbalance in esophageal inhibition and contraction in JE.

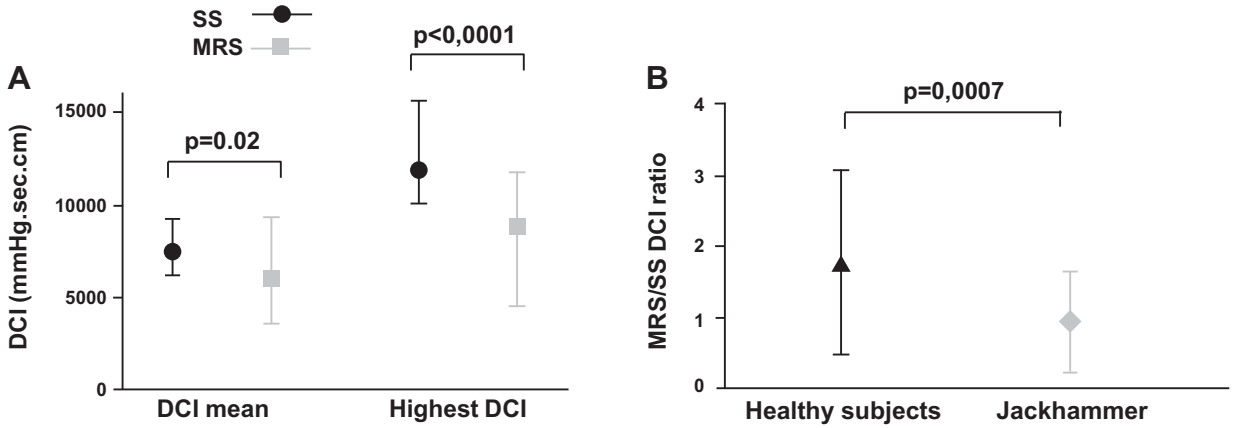

Fig. 2. *A*: mean and highest distal contractile integral (DCI) was lower after multiple rapid swallows (MRS) than after single swallows (SS) in jackhammer esophagus (JE) patients. *B*: MRS-to-SS DCI ratio was lower in JE patients than in healthy subjects.

JE patients (66%) had an MRS-to-SS DCI ratio < 1. MRS-to-SS DCI ratios were significantly lower than those obtained in our cohort of asymptomatic controls [0.8 (0.5–1.1) vs. 1.2 (1.1–2.3); $P = 0.0007$] (Fig. 2*B*). Contrary to what we have observed in our controls, peristaltic sequences after MRS were faster and more premature than those observed after SS (Table 1). The same was observed when we compared normal sequences with hypercontractile ones after MRS [CFV: 4.4 cm/s (3.0–6.7) vs. 3.0 cm/s (2.5–4.2); $P = 0.002$] and DL [5.8 (4.8–6.8) vs 7.1 s (6.2–7.5); $P = 0.003$].

When JE patients with normal inhibition during MRS were compared with patients who had abnormal motor inhibition, mean DCI after SS was lower in those with normal inhibition [7,395 (6,056–9,678) compared with those having abnormal inhibition [8,214 (7,528–10,901) mmHg·cm·s; $P = 0.038$]. Mean DCI after MRS, however, was similar between these two subgroups [6,127 (3,878–9,847) vs. 6,357 (3,208–10,671) mmHg·cm·s; $P = 0.77$]. The MRS-to-SS DCI ratio was also similar [0.9 (0.6–1.3) vs. 0.9 (0.5–1.1); $P = 0.26$].

Rapid Drink Challenge

Of the 83 JE patients, 34 (41%) successfully completed RDC [21 with 200 ml of water and 13 with 100 ml of water (Table 2)]. Dysphagia and chest pain were the predominant symptoms in this subset (58 and 44%) similarly to the whole cohort. Of the remaining 49 patients, 12 did have RDC data because RDC was not incorporated into routine HRM in one of the Centers; 37 did not have RDC data because patients either refused to perform the test or did not perform it adequately, or physicians considered it risky for aspiration. All 34 patients performed the RDC with a median drinking time similar to those previously reported (20). Interestingly, 19 patients had at least three pressurization events, the median percentage time at 20 mmHg during the 100- and 200-ml RDC being 10 and 17%, respectively. Moreover there was increase in the pressure gradient across the EGJ during both the 100- (0.7 mmHg; −1.8 to 4.9) and 200-ml (4.8 mmHg; −2.8 to 11.5) RDC, despite the fact that mean IRP remained within the range of normal.

Table 2. *High-resolution manometry variables during and after rapid drinking challenge with either 100 or 200 ml of water in jackhammer esophagus patients*

RDC Parameters	100 ml RDC		200 ml RDC	
	JE patients	Healthy controls (21)	JE patients	Healthy controls (21)
N	13	17	21	73
RDC performance				
Time, s	11 (3); 8–17	8–26	29 (14); 14–64	12–47
Pressure response during RDC				
Pressurization at 20 mmHg	1 (2); 0–7*	0–0	2 (3); 0–9*	0–2
Time at 20 mmHg, %	10 (58); 6–67*	0–0	17 (28); 0–66*	0–8
Mean IRP, mmHg	5.8 (6); 0–17.1	−3 to 8	6.7 (7); 2.9–19.3	−2 to 12
Gradient across EGJ, mmHg	0.7 (6.8); −3.6 to 14.8*	−10 to 1	4.8 (14); −8 to 35.2*	−6 to 4
Activity after RDC†				
CFV, cm/s	4.1 (2.5); 1.1–18.2	1–18	5.3 (6); 0.9–21.4	1–14
DL, s	8 (5.3); 3.4–14	N/A	5 (3); 1.8–7.5	N/A
DCI, mmHg·cm·s	5,680 (9,813); 448–26,271*	61–3,877	3,903 (7,975); 1,376–64,904*	206–6,557
RDC-to-SS DCI ratio	0.7 (1.5); 0.1–2.9	0.05–2.68	0.6 (0.9); 0.1–9.2*	0.1–2.9

Values for jackhammer esophagus (JE) patients are medians (interquartile ranges); full range. Values for healthy controls are 5−95th confidence intervals (CI). CFV, contraction front velocity; DCI, distal contractile integral; DL, distal latency; EGJ, esophagogastric junction; IRP, integrated relaxation pressure; MRS, multiple rapid swallows; N/A, not available; RDC, rapid drinking challenge; SS, single swallows. †In 9 of 13 patients after 100 ml and 12 of 21 patients after 200 ml; *RDC variables outside the normative range as reported by Marin and Serra (21) (95th CI for all variables except for RDC-to-SS DCI ratio, where the 5th CI was considered).

Nineteen patients were outside the upper limit of normal range for number of pressurizations, twenty for percentage of time at 20 mmHg, and 10 for pressure gradient across EGJ. At least one of the 3 variables was out of range in 25 patients (74%). Of 34 patients, 21 (62%) demonstrated a contraction at the end of the RDC, of which 8 (38%) were hypercontractile (4 after 100 ml and 4 after 200 ml). The RDC-to-SS ratio was <1 in 13 of the 21 patients (62%).

Relationship Between Motor Function and Presenting Symptoms

The highest DCI after SS was higher in patients with dysphagia compared with those without [12,385 (10,577–19,670) vs. 11,192 (9,500–14,278) mmHg·cm·s; $P = 0.04$]. Furthermore, the gradient across the EGJ during RDC was also higher in the dysphagia group than in patients without dysphagia [5 (2.4–9.8) vs. −2 (−4.4 to 0) mmHg; $P = 0.01$]. No relationships were observed between motor variables and chest pain.

DISCUSSION

In this study evaluating esophageal physiology and pathophysiology in JE using provocative tests, we demonstrate that there is abnormal inhibition during MRS and RDC, but not in all JE patients. More interestingly, JE patients appear to be more strongly stimulated after SS than after MRS, with no significant augmentation of contraction following MRS and RDC, fulfilling criteria for lack of contraction reserve despite presence of smooth muscle contraction after provocative testing. Our findings suggest that esophageal motor physiology is abnormal in JE patients, with inappropriately exaggerated excitatory influences in the majority, combined with abnormal inhibitory function in some JE patients. Finally, despite relaxation of the LES (as evidenced by normal IRP), an obstructive pattern was noted with RDC in some JE patients.

Both excitatory and inhibitory influences need to be present in a balanced fashion for normal esophageal function during swallowing. The most obvious consequences of abnormal inhibition consist of abnormal sequencing of esophageal body peristalsis (resulting in premature sequences) and abnormal LES relaxation after SS. However, abnormal inhibition has also been described when esophageal contraction demonstrates prolonged duration and multiple contraction peaks (32). Using MRS, we found abnormality of inhibitory function in some but not all of our JE patients and, interestingly, DCI after SS was higher in these patients compared with those having normal inhibitory function. This finding, in agreement with previous data in a broader spectrum of hypercontractile motility patients (27), may suggest two different groups of JE from a pathophysiological perspective. On the whole, the difference in prevalence of defective inhibition between our JE patients and our cohort of asymptomatic controls (i.e., 48 vs. 24%) did not reach statistical significance, possibly because of the low number of controls, although difference in contractile integral was statistically significant. Furthermore, another control series in the literature has shown that defective inhibition was present in only 5% of healthy controls (12). The finding of abnormal inhibition even in healthy controls suggests that there is inherent variation in refractoriness of the esophageal muscle to contraction during repetitive swallowing. Despite this, the frequency of abnormal inhibition was higher in patients with JE. However, we have to point out that normative values are based on small cohorts of healthy subjects and therefore no clear thresholds of motor inhibition are available in literature. Regardless, the inhibitory abnormality in JE is heterogenous and variable; more abnormal and homogeneous inhibitory dysfunction would likely shift the diagnosis toward more severe motor disorders, i.e., type 3 achalasia, diffuse esophageal spasm, or abnormal LES relaxation.

Abnormally increased excitation has been described in patients with nutcracker esophagus (8) in some of the early HRM studies as merging of the two smooth muscle contraction segments, leading to a single exaggerated contraction in the distal esophageal body. Korsapati et al. (18) has shown that presence of muscular asynergy (peak longitudinal muscle contraction occurring earlier than peak circular muscle contraction) during SS in similar nutcracker patients was due to a hypercholinergic state because with high-frequency esophageal ultrasound, it was observed to revert after infusion of atropine. Chicago Classification criteria for JE identify the most extreme end of the hypercontractile spectrum, such that many patients with nutcracker esophagus do not fulfil criteria for JE (24). Our findings support the concept that the esophagus is strongly stimulated with SS in JE. Physiologically, esophageal smooth muscle, when provoked, is able to increase contraction vigor. This is the so-called contraction reserve. However, in JE, the muscle is not able to increase contraction vigor even when provoked with MRS because it is strongly stimulated with just SS (Fig. 2*B*), even though the vigor of smooth muscle contraction following MRS in JE is higher than that seen in normal controls. We believe that the lack of contraction reserve could suggest a primary motor hyperstimulatory mechanism rather than an obstructive secondary response where further increase in esophageal contraction could be possible. However, this is speculative, as we excluded patients with identified secondary obstructive processes on esophageal testing. Furthermore, the observation that hypercontractility was less common and latencies were shorter after MRS than after SS in JE confirms that regulation of timing and strength of contraction after MRS is different from that triggered by SS.

It is well known that there is swallow-to-swallow variation in esophageal motor metrics. This is most profound in motor disorders that are not well developed, in contrast to profound and well-developed motor disorders such as achalasia types 1 and 2 and absent contractility. In fact, these well-developed motor disorders demonstrate a remarkable consistency and reproducibility in response to both SS and provocative testing, especially MRS (27). In contrast, less-developed motor disorders demonstrate variation among SS, requiring finite criteria for diagnosis (e.g., 20% premature with distal esophageal spasm, 20% hypercontractile with JE). In this setting the response to provocative testing is useful, as the contractile response appears less variable, even though motor inhibition remains heterogeneous (27).

Our study provides important information about the behavior of JE patients during RDC and the relationship between motor abnormalities and symptoms. Our results have shown that a considerable proportion of patients who underwent RDC had alterations in the esophageal body and/or a high EGJ pressure gradient suggesting latent obstruction. Previous data in the literature in smaller groups of patients are in line with

our findings. Marin and Serra (21) described the response to RDC in 14 JE patients, concluding that they had a certain degree of pressurization associated with a minimal increment of the EGJ pressure gradient and a valid LES relaxation. Ang et al. (2) have shown pressurization in 64.7% of 17 patients with either JE or esophageal spasm during RDC; the presence of esophageal pressurization suggests the presence of an EGJ pressure gradient even though this was not reported. Although IRP remains a robust metric during SS, its performance has not been specifically tested during provocative testing; on the contrary, trans-EGJ pressure gradient is often reported as an outcome measure for RDC, either indirectly in terms of pressurization (2, 21) or directly as the trans-EGJ pressure gradient (20, 21). It is interesting to note that, in our series, dysphagia was present in those patients with higher DCIs after SS, and particularly those with higher values of EGJ pressure gradient, giving a clinical perspective to our findings. This latter subgroup of patients may have an advanced motor disorder, and the increase of resistance to outflow may be related to a primary motor obstruction (i.e., achalasia) that is not completely expressed phenotypically. Indeed, previous studies have shown that increase of peripheral resistance may lead to increase of peristaltic vigor (5, 10). However, early identification of patients that may progress to achalasia could be difficult with HRM, given that IRP is normal during both SS and RDC. These data have been also highlighted in the paper by Ang et al. (3), where IRP was increased during RDC in only 1 of 17 JE patients (6%). Therefore, the use of EGJ pressure gradient could be of better value in this regard. The observation that some patients have latent obstruction on RDC may explain why performing a POEM procedure without involving the LES has resulted in incomplete relief of dysphagia, whereas if the LES was also included in the POEM, symptom relief was more consistent.

Some methodological points and limitations need further discussion, first of which is the number of MRS performed. Most of our patients underwent two MRS tests. In a recent paper from our group, we suggested that three MRS is the most optimal number to obtain reliable data regarding contraction reserve (23). However, those results were obtained in a different setting (i.e., ineffective esophageal motility and normal motility patients) with patients who have higher variability among MRS series, whereas reproducibility with two MRS series has been previously shown as adequate in hypermotility patients (27). Regarding reliable evaluation of motor inhibition, we have previously shown that only one MRS test is sufficient (22). Second, we did not perform RDC in all our JE patients and did not have a control group of our own for RDC. Therefore, data about relationship between symptoms and obstructive parameters during RDC should be interpreted with caution. However, on one hand it needs to be acknowledged that performance of RDC cannot be expected in all patients because of patients' refusal, inability to do it adequately, or safety, especially in the elderly; nevertheless, our RDC subgroup had similar clinical presentation to the one of the whole cohort and a size that was still the biggest of the literature. On the other hand, the reference values that we have used have been obtained with the same protocol and equipment used in our study, with a similar cohort size as our patients' group (22). Therefore, we feel our findings are representative of esophageal physiology in JE despite these limitations.

Finally, data about opioid medication use was not available in our series. It is known from the literature that opioids alter esophageal motility by decreasing inhibitory function at the level of LES (26). Hypercontractile effect in the esophageal body is less evident (19, 29); therefore, we do not feel that this detracts from our overall conclusion of pathophysiological mechanisms in JE.

In conclusion, our data with MRS and RDC suggest altered neural control in JE patients with heterogeneity in inhibitory function. Furthermore, some patients had latent EGJ obstruction during RDC, which correlates with dysphagia. Performing RDC during HRM studies, therefore, may also guide optimal therapeutic strategies.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

A.M. and R.P. conceived and designed the research; A.M., F.Q., S.T., E.S., N.D.B., and M.F. performed experiments; A.M., F.Q., S.T., E.S., N.D.B., C.P.G., and R.P. analyzed data; A.M., F.Q., S.T., E.S., N.D.B., M.F., C.P.G., and R.P. interpreted results of experiments; A.M. prepared figures; A.M., C.P.G., and R.P. drafted manuscript; A.M., E.S., C.P.G., and R.P. edited and revised manuscript; A.M., F.Q., S.T., E.S., N.D.B., M.F., C.P.G., and R.P. approved final version of manuscript.

REFERENCES

1. **Achem SR, Kolts BE, Wears R, Burton L, Richter JE.** Chest pain associated with nutcracker esophagus: a preliminary study of the role of gastroesophageal reflux. *Am J Gastroenterol* 88: 187–192, 1993.
2. **Ang D, Hollenstein M, Misselwitz B, Knowles K, Wright J, Tucker E, Sweis R, Fox M.** Rapid Drink Challenge in high-resolution manometry: an adjunctive test for detection of esophageal motility disorders. *Neurogastroenterol Motil* 29: e12902, 2017. doi:10.1111/nmo.12902.
3. **Bechara R, Ikeda H, Inoue H.** Peroral endoscopic myotomy for Jackhammer esophagus: to cut or not to cut the lower esophageal sphincter. *Endosc Int Open* 4: E585–E588, 2016. doi:10.1055/s-0042-105204.
4. **Behar J, Biancani P.** Pathogenesis of simultaneous esophageal contractions in patients with motility disorders. *Gastroenterology* 105: 111–118, 1993. doi:10.1016/0016-5085(93)90016-6.
5. **Brink GJ, Lei WY, Omari TI, Singendonk MMJ, Hung JS, Liu TT, Yi CH, Chen CL.** Physiological augmentation of esophageal distension pressure and peristalsis during conditions of increased esophageal emptying resistance. *Neurogastroenterol Motil* 30: e13225, 2018. doi:10.1111/nmo.13225.
6. **Brito EM, Camacho-Lobato L, Paoletti V, Gideon M, Katz PO, Castell DO.** Effect of different swallow time intervals on the nutcracker esophagus. *Am J Gastroenterol* 98: 40–45, 2003. doi:10.1111/j.1572-0241.2003.07181.x.
7. **Burton PR, Brown W, Laurie C, Richards M, Afkari S, Yap K, Korin A, Hebbard G, O'Brien PE.** The effect of laparoscopic adjustable gastric bands on esophageal motility and the gastroesophageal junction: analysis using high-resolution video manometry. *Obes Surg* 19: 905–914, 2009. doi:10.1007/s11695-009-9845-3.
8. **Clouse RE, Staiano A.** Topography of normal and high-amplitude esophageal peristalsis. *Am J Physiol Gastrointest Liver Physiol* 265: G1098–G1107, 1993. doi:10.1152/ajpgi.1993.265.6.G1098.
9. **Clouse RE, Staiano A, Alrakawi A.** Development of a topographic analysis system for manometric studies in the gastrointestinal tract. *Gastrointest Endosc* 48: 395–401, 1998. doi:10.1016/S0016-5107(98)70010-0.
10. **Dodds WJ, Hogan WJ, Stewart ET, Stef JJ, Arndorfer RC.** Effects of increased intra-abdominal pressure on esophageal peristalsis. *J Appl Physiol* 37: 378–383, 1974. doi:10.1152/jappl.1974.37.3.378.
11. **Dogan I, Puckett JL, Padda BS, Mittal RK.** Prevalence of increased esophageal muscle thickness in patients with esophageal symptoms. *Am J Gastroenterol* 102: 137–145, 2007. doi:10.1111/j.1572-0241.2006.01003.x.
12. **Elvevi A, Mauro A, Pugliese D, Bravi I, Tenca A, Consonni D, Conte D, Penagini R.** Usefulness of low- and high-volume multiple rapid

swallowing during high-resolution manometry. *Dig Liver Dis* 47: 103–107, 2015. doi:10.1016/j.dld.2014.10.007.

13. **Fornari F, Bravi I, Penagini R, Tack J, Sifrim D.** Multiple rapid swallowing: a complementary test during standard oesophageal manometry. *Neurogastroenterol Motil* 21: 718–e41, 2009. doi:10.1111/j.1365-2982.2009.01273.x.
14. **Grigolon A, Consonni D, Bravi I, Tenca A, Penagini R.** Diagnostic yield of 96-h wireless pH monitoring and usefulness in patients' management. *Scand J Gastroenterol* 46: 522–530, 2011. doi:10.3109/00365521.2010.545834.
15. **Gyawali CP.** Achalasia: new perspectives on an old disease. *Neurogastroenterol Motil* 28: 4–11, 2016. doi:10.1111/nmo.12750.
16. **Gyawali CP, Kushnir VM.** High-resolution manometric characteristics help differentiate types of distal esophageal obstruction in patients with peristalsis. *Neurogastroenterol Motil* 23: 502–e197, 2011. doi:10.1111/j.1365-2982.2011.01672.x.
17. **Kahrilas PJ, Bredenoord AJ, Fox M, Gyawali CP, Roman S, Smout AJ, Pandolfino JE; International High Resolution Manometry Working Group.** The Chicago Classification of esophageal motility disorders, v3.0. *Neurogastroenterol Motil* 27: 160–174, 2015. doi:10.1111/nmo.12477.
18. **Korsapati H, Bhargava V, Mittal RK.** Reversal of asynchrony between circular and longitudinal muscle contraction in nutcracker esophagus by atropine. *Gastroenterology* 135: 796–802, 2008. doi:10.1053/j.gastro.2008.05.082.
19. **Kraichely RE, Arora AS, Murray JA.** Opiate-induced oesophageal dysmotility. *Aliment Pharmacol Ther* 31: 601–606, 2010. doi:10.1111/j.1365-2036.2009.04212.x.
20. **Marin I, Cisternas D, Abrao L, Lemme E, Bilder C, Ditaranto A, Coello R, Hani A, Leguizamo AM, Meixueiro A, Remes-Troche J, Zavala MA, Ruiz de León A, Perez de la Serna J, Valdovinos MA, Serra J.** Normal values of esophageal pressure responses to a rapid drink challenge test in healthy subjects: results of a multicenter study. *Neurogastroenterol Motil* 29: e13021, 2017. doi:10.1111/nmo.13021.
21. **Marin I, Serra J.** Patterns of esophageal pressure responses to a rapid drink challenge test in patients with esophageal motility disorders. *Neurogastroenterol Motil* 28: 543–553, 2016. doi:10.1111/nmo.12749.
22. **Mauro A, Elvevi A, Consonni D, Franchina M, Pugliese D, Tenca A, Conte D, Penagini R.** Reliability of a single multiple rapid swallowing sequence during high resolution manometry (Abstract). *UEG Journal* 2 (*Suppl* 1): A286, 2015.
23. **Mauro A, Savarino E, De Bortoli N, Tolone S, Pugliese D, Franchina M, Gyawali CP, Penagini R.** Optimal number of multiple rapid swallows needed during high-resolution esophageal manometry for accurate prediction of contraction reserve. *Neurogastroenterol Motil* 30: e13253, 2018. doi:10.1111/nmo.13253.
24. **Mello MD, Duraiswamy S, Price LH, Li Y, Patel A, Gyawali CP.** Exaggerated smooth muscle contraction segments on esophageal high-resolution manometry: prevalence and clinical relevance. *Neurogastroenterol Motil* 27: 229–236, 2015. doi:10.1111/nmo.12471.
25. **Pandolfino JE, Ghosh SK, Rice J, Clarke JO, Kwiatek MA, Kahrilas PJ.** Classifying esophageal motility by pressure topography characteristics: a study of 400 patients and 75 controls. *Am J Gastroenterol* 103: 27–37, 2008. doi:10.1111/j.1572-0241.2007.01532.x.
26. **Penagini R, Picone A, Bianchi PA.** Effect of morphine and naloxone on motor response of the human esophagus to swallowing and distension. *Am J Physiol Gastrointest Liver Physiol* 271: G675–G680, 1996. doi:10.1152/ajpgi.1996.271.4.G675.
27. **Price LH, Li Y, Patel A, Gyawali CP.** Reproducibility patterns of multiple rapid swallows during high resolution esophageal manometry provide insights into esophageal pathophysiology. *Neurogastroenterol Motil* 26: 646–653, 2014. doi:10.1111/nmo.12310.
28. **Pugliese D, Mauro A, Consonni D, Bravi I, Tenca A, Elvevi A, Conte D, Penagini R.** pH Impedance vs. traditional pH monitoring in clinical practice: an outcome study. *J Gastroenterol* 51: 130–137, 2016. doi:10.1007/s00535-015-1090-z.
29. **Ratuapli SK, Crowell MD, DiBaise JK, Vela MF, Ramirez FC, Burdick GE, Lacy BE, Murray JA.** Opioid-Induced Esophageal Dysfunction (OIED) in patients on chronic opioids. *Am J Gastroenterol* 110: 979–984, 2015. doi:10.1038/ajg.2015.154.
30. **Roman S, Tutuian R.** Esophageal hypertensive peristaltic disorders. *Neurogastroenterol Motil* 24, *Suppl* 1: S32–S39, 2012. doi:10.1111/j.1365-2982.2011.01837.x.
31. **Shaker A, Stoikes N, Drapekin J, Kushnir V, Brunt LM, Gyawali CP.** Multiple rapid swallow responses during esophageal high-resolution manometry reflect esophageal body peristaltic reserve. *Am J Gastroenterol* 108: 1706–1712, 2013. doi:10.1038/ajg.2013.289.
32. **Sifrim D, Janssens J, Vantrappen G.** Failing deglutitive inhibition in primary esophageal motility disorders. *Gastroenterology* 106: 875–882, 1994. doi:10.1016/0016-5085(94)90745-5.
33. **Spechler SJ, Castell DO.** Classification of oesophageal motility abnormalities. *Gut* 49: 145–151, 2001. doi:10.1136/gut.49.1.145.
34. **Stoikes N, Drapekin J, Kushnir V, Shaker A, Brunt LM, Gyawali CP.** The value of multiple rapid swallows during preoperative esophageal manometry before laparoscopic antireflux surgery. *Surg Endosc* 26: 3401–3407, 2012. doi:10.1007/s00464-012-2350-0.