Characteristics of Consecutive Esophageal Motility Diagnoses After a Decade of Change

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Background and Aims: Combined multichannel intraluminal impedance and esophageal manometry (MII-EM) measures concomitantly bolus transit and pressure changes allowing determination of the functional impact of esophageal motility abnormalities. Ten years ago our laboratory reported MII-EM results in 350 consecutive patients. Since then high-resolution impedance manometry (HRIM) became available and the definitions of ineffective esophageal motility (IEM) and nutcracker esophagus were revised. The aim of this study was to assess the impact of these developments on esophageal function testing.

Methods: From August 2012 through May 2013, HRIM was performed in 350 patients referred for esophageal function testing. Each patient received 10 liquid and 10 viscous swallows. While taking advantage of the new technology and revised criteria, HRIM findings were classified according to the conventional criteria to allow more appropriate comparison with our earlier analysis.

Results: Compared with the study performed 10 years ago, the prevalence of normal manometry (36% vs. 35%), achalasia (7% vs. 8%), scleroderma (1% vs. 1%), hypertensive lower esophageal sphincter (LES) (7% vs. 7%), and hypotensive LES (1% vs. 2%) remained the same, whereas the prevalence of distal esophageal spasm (9% vs. 3%), nutcracker esophagus (9% vs. 3%), and poorly relaxing LES (10% vs. 3%) decreased and the prevalence of IEM increased (20% vs. 31%) significantly. Compared with the early study, normal liquid bolus transit was significantly different in patients with hypertensive LES (96% vs. 57%) and poorly relaxing LES (55% vs. 100%).

Conclusions: This study brings to light the increase in prevalence of IEM. In addition, it suggests that the hypertensive LES and poorly relaxing LES may each affect bolus transit in about half of these patients.

Key Words: esophagus, motility, ineffective esophageal motility

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Combined multichannel intraluminal impedance and manometry (MII-EM) is a test of esophageal function that provides concomitant evaluation of bolus transit and pressure changes. First described by Silny in 1991, MII uses differences in resistance to alternating currents among air, esophageal mucosa, and esophageal liquid bolus to detect bolus movement within the esophagus without the use of radiation.[1] Impedance is a useful addition to traditional esophageal liquid manometry testing as it provides bolus transit information in addition to pressure data, and normal values have been established for MII-EM.[2] The classification of esophageal motility abnormalities has evolved since Spechler and Castell's original classification based on manometry alone in 2001,[3] specifically the diagnostic criteria of ineffective esophageal motility (IEM) and the nutcracker esophagus have become more stringent.[4,5] Furthermore, high-resolution impedance manometry (HRIM), through more closely spaced pressure sensors along the catheter, allows more detailed measurements of the intraluminal pressures and through the color-coded pressure topography, provides a more accurate evaluation of the lower esophageal sphincter (LES) dynamics following deglutition.

The interpretation of HRIM is still being refined. Because the data gathered from the pressure topography is user dependent, many clinicians convert the topography display back to convention line tracings. Thus, using all the tools available with this exciting technique allows for a more standardized measurement and ease in establishing a diagnosis.

Ten years ago, 350 consecutive patients were evaluated in the Medical University of South Carolina esophageal motility laboratory for functional abnormalities using combined conventional MII-EM with intraluminal transducers at 5-cm intervals.[6] The aim of the current study was to evaluate and update the demographics and prevalence of the various manometric disorders with the updated definitions of IEM and the nutcracker esophagus, in addition to the increased accuracy provided by HRIM technology.

METHODS

This study retrospectively examined 350 consecutive prospectively collected HRIM studies performed in the esophageal laboratory at the Medical University of South Carolina from August 3, 2012 to May 15, 2013. Approval was obtained from our Institutional Review Board to review and analyze these studies and to publish the information obtained from them. All patients included in the study provided informed consent, giving the investigators permission to use their data for database research studies.

Esophageal function testing was performed using a UNI-ESO-WG1A1 High-Resolution Impedance Manometry Probe (Sandhill Scientific Inc., Highlands Ranch, CO). The UNI-ESO-WG1A1 HRIM catheter has a 4 mm diameter and includes 32 circumferential pressure channels and 16 impedance channels. Solid state intraluminal pressure transducers are located at −6, −4, −3, −2, −1, 0, 1,

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2, 3, 4, 5, 6, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 19, 20, 21, 23, 24, 25, 26, 27, 28, 29, and 30 cm and impedance-measuring segments at −5, −3, −1, 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, and 25 cm. The catheter was passed transnasally so that the zero point on the catheter was aligned with the maximal high-pressure zone of the LES. In the supine position, patients received 10 swallows of 5 mL normal saline and 10 swallows of 5 mL viscous (apple sauce–like consistency) material each 20 to 30 seconds apart. The HRIM software can display data in either color-coded pressure topography Clouse plots or traditional waveform line plots. In this study, all data were acquired and visually assessed by HRIM, but numerically analyzed using conventional waveform line plots and interpreted using conventional manometry normals to standardize data analysis for comparison with our prior study of diagnostic distribution a decade earlier.[6]

Manometric parameters used to characterize swallows included: (1) contraction amplitude at 5 and 10 cm above the LES; (2) distal esophageal amplitude (DEA) as the average of contraction amplitude at 5 and 10 cm above the LES; and (3) onset velocity of esophageal contractions in the distal part of the esophagus (ie, contraction velocity between 10 and 5 cm above the LES). Mid-respiratory resting pressure and LES residual pressure during swallowing were used to assess LES function. Impedance parameters included (1) bolus entries and exits 5, 10, 15, and 20 cm above the LES; and (2) total bolus transit time (TBTT), the time elapsed between bolus entry at 20 cm above the LES and bolus exit at 5 cm above the LES.

Swallows were classified by manometry as (1) normal, if the contraction amplitudes 5 and 10 cm above the LES were each ≥30 mm Hg and the distal-onset velocity was <8 cm/s; (2) ineffective, if either of the contraction amplitudes at 5 or 10 cm above the LES was <30 mm Hg; or (3) simultaneous, if the contraction amplitudes at 5 and 10 cm above the LES were each ≥30 mm Hg and the distal-onset velocity was >8 cm/s.

Swallows were classified by MII as showing complete bolus transit if bolus entry occurred at 20 cm above the LES; bolus exit points were recorded in the 3 distal impedance-measuring sites at 15, 10, and 5 cm above the LES, and the TBTT was <15 seconds. A swallow was classified as incomplete bolus transit if bolus exit was not identified at any of the 3 distal impedance-measuring sites, if bolus entry was not identified at 20 cm above the LES, or if the TBTT was >15 s. Overall, esophageal transit was defined as normal liquid transit if at least 80% of liquid swallows had complete bolus transit and as normal viscous transit if at least 70% of viscous swallows had complete bolus transit.[2]

Manometry was evaluated for liquid swallows only because that has been standard worldwide for many years. Bolus transit, however, was evaluated for both liquid and viscous swallows. Diagnoses of manometric motility abnormalities for 8 "named" entities were established using the original criteria published by Spechler and Castell,[3] along with the more recently suggested changes in diagnostic criteria for IEM[4] and the nutcracker esophagus.[5] Achalasia was defined by absent esophageal body peristalsis and if present, poorly relaxing LES (residual pressure >8 mm Hg). The occasional hypertensive resting LES pressure reinforced this diagnosis. Scleroderma (SSc) was defined based on an appropriate clinical diagnosis and confirmed by low-amplitude contractions in the distal esophagus with or without a low LES pressure. Distal esophageal spasm (DES) was defined as ≥20% simultaneous contractions. IEM was defined as ≥50% swallows with contraction amplitude of <30 mm Hg in either of the 2 distal sites located at 5 and 10 cm above the LES. Mild IEM was defined by associated normal bolus transit for both liquid and viscous swallows, moderate IEM by abnormal bolus transit for either liquid or viscous swallows, and severe IEM by abnormal bolus transit for both liquid and viscous swallows. Nutcracker esophagus was defined as normal peristalsis of the esophageal body with an average DEA exceeding 220 mm Hg. Poorly relaxing LES was defined as average LES residual pressure exceeding 8 mm Hg associated with normal esophageal body contractions. Hypertensive LES was defined as an LES mid-respiratory resting pressure exceeding 45 mm Hg with normal esophageal body contractions. Normal esophageal manometry was defined as no more than 40% ineffective swallows, no more than 10% simultaneous swallows, a DEA < 220 mm Hg, and a normal LES resting and residual pressures. In patients having both esophageal body and LES abnormalities, the final diagnosis was based on the esophageal body finding.

Major motility abnormality (MMA) is a MII-EM diagnosis that has evolved in our laboratory over the past 10 years; that is, since our prior report on diagnostic findings in the initial group of 350 patients. It is reserved for patients whose motility study is clearly abnormal but difficult to simply categorize into one of the 8 "named" motility abnormalities. It is also intended to inform the referring physician that the study is definitely abnormal. The final diagnosis on the report reads as "Major motility abnormality with features of – and –" and may include any combination of the following: achalasia, SSc, IEM, DES, or nutcracker esophagus. It is intended to be used sparingly. Figure 1 is a pressure tracing in which 90% of swallows show failed peristalsis, 10% of swallows are ineffective, and there is a normal residual pressure. This reading was read as "MMA with features of achalasia and IEM." In this case, barium esophagram failed to reveal the classic features of achalasia.

Patients were asked to fill out a questionnaire in which they described their major symptom, which was the reason for undergoing MII-EM. The symptoms included heartburn, dysphagia, regurgitation, chronic cough, chest pain or pressure, epigastric pain, hoarseness, throat clearing, and recurrent asthma attacks.

Simple statistics were used to describe manometric and impedance characteristics in this group of patients. χ^2 tests were used to assess differences in proportion of patients and/or swallows. Unpaired *t* tests were used to compare mean values of different diagnostic groups. For statistical significance α was set at 0.05.

RESULTS

Three hundred and fifty patients (223 female, 116 male, mean age: 57.3 y, range 16 to 84 y) underwent esophageal function testing using HRIM between August 2012 and May 2013. While all patients received liquid swallows, 46 patients (10 normal manometry, 10 achalasia, 2 DES, 2 nutcracker, 13 IEM, 2 SSc, 3 hypertensive LES, 1 hypotensive LES, 3 MMA) requested discontinuation of the study before receiving viscous swallows. The primary symptoms for which patients were referred for esophageal function testing were: dysphagia (28%), chronic cough

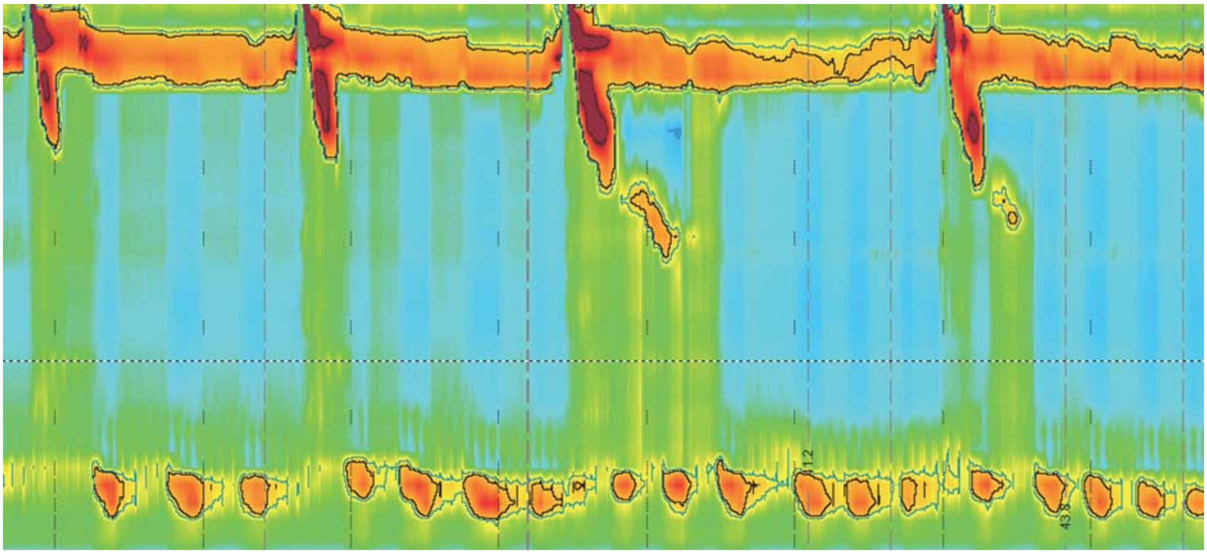

FIGURE 1. Major motility abnormality with features of achalasia and ineffective esophageal motility.

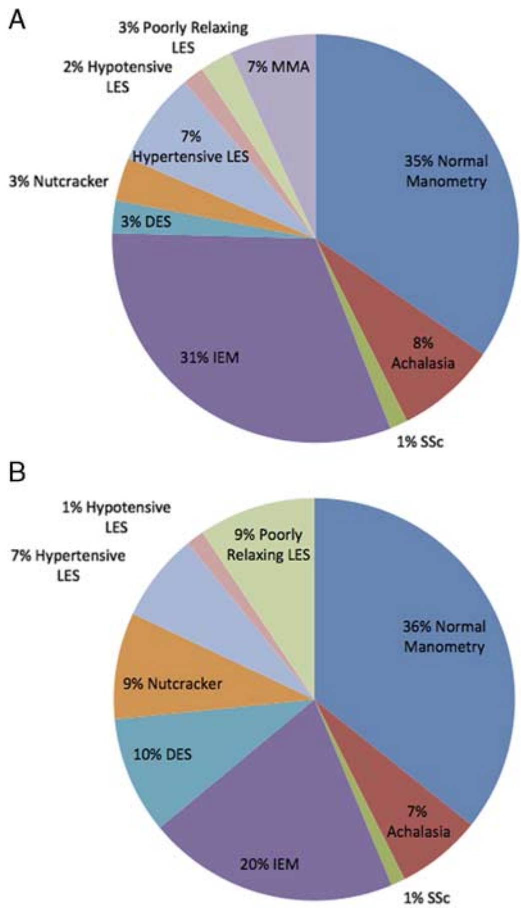

FIGURE 2. A, Manometric diagnoses 2012 to 2013. B, Manometric diagnoses 2002 to 2003. DES indicates distal esophageal spasm; IEM, ineffective esophageal motility; LES, lower esophageal sphincter; MMA, major motility abnormality; SSc, scleroderma.

(15%), chest pain/pressure (12%), heartburn (11%), regurgitation (11%), epigastric pain (6%), throat clearing (6%), hoarseness (3%), asthma (3%), and other (6%). Dysphagia was the primary presenting symptom for patients diagnosed with achalasia (68%), nutcracker esophagus (33%), SSc (80%), DES (44%), and hypertensive LES (42%). The primary presenting symptom of IEM was cough (18%), hypotensive LES was regurgitation (33%) and cough (33%), and poorly relaxing LES was chest pain (22%) and cough (22%). Of the 76 patients presenting with dysphagia who had both liquid and viscous swallows performed, 28 (37%) had normal bolus transit, 2

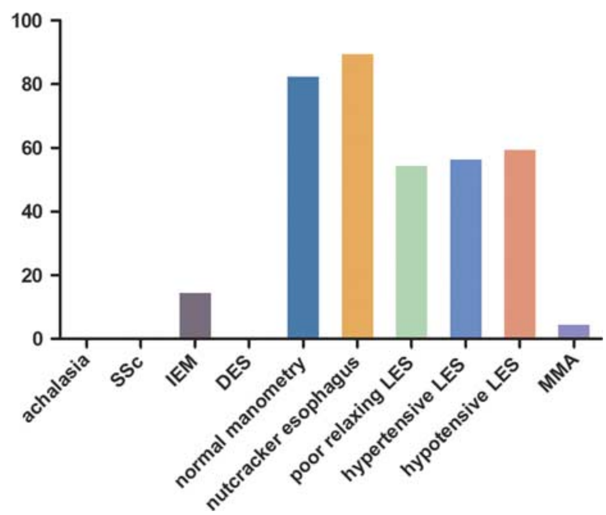

FIGURE 3. Percentage of patients with normal bolus transit for liquid swallows based on manometric diagnoses. DES indicates distal esophageal spasm; IEM, ineffective esophageal motility; LES, lower esophageal sphincter; MMA, major motility abnormality; SSc, scleroderma.

(3%) had abnormal bolus transit for liquid swallows, 4 (5%) had abnormal bolus transit for viscous swallows, and 42 (55%) had abnormal bolus transit for both liquid and viscous swallows.

Detailed demographic features of all patients are shown in Table 1. Patients with IEM, nutcracker, hypertensive LES, and normal manometry were more frequently women (67%, 92%, 69%, 76%). However, only the prevalence of females with nutcracker esophagus was significantly different from the prevalence of females diagnosed with other esophageal abnormalities at the laboratory ($P < 0.03$). Patients across all categories were more frequently white; however, no single diagnosis was significantly different when compared with patients with other esophageal abnormalities.

Manometric Findings Using Liquid Swallows 2012 to 2013

Of the 350 patients receiving liquid swallows, 121 (35%) had normal EM. On the basis of the above-mentioned manometric criteria, 28 (8%) had achalasia, 5 (1%) SSc, 110 (31%) IEM, 9 (3%) DES, 12 (3%) nutcracker esophagus, 26 (7%) hypertensive LES, 6 (2%) hypotensive LES, 9 (3%) poorly relaxing LES, and 24 (7%) MMA (Fig. 2A).

Manometric Findings Using Liquid Swallows 2002 to 2003

Ten years ago, of the 350 patients who received liquid swallows from our laboratory, 125 (36%) had normal EM, 24 (7%) achalasia, 4 (1%) SSc, 71 (20%) IEM, 33 (9%) DES, 30 (9%) nutcracker esophagus, 25 (7%) hypertensive LES, 5 (1%) hypotensive LES, and 33 (9%) poorly relaxing LES (Fig. 2B).

Combined Manometry and Impedance Findings 2012 to 2013

Figure 3 depicts the percentage of patients for each manometric diagnosis that had normal bolus transit for liquid swallows. Combined MII-EM for liquid swallows revealed that none of the patients with achalasia, SSc, or DES had normal bolus transit. Fifteen percent of patients with IEM had normal bolus transit, whereas a little over half of patients with hypertensive LES (57%), hypotensive LES (60%), and poorly relaxing LES (55%) had normal liquid bolus transit. Most patients with normal manometry (83%) and nutcracker esophagus (90%) had normal bolus transit for liquids.

Combined Manometry and Impedance Findings 2002 to 2003

Our laboratory's previous study of combined MII-EM information for liquid swallows showed that none of the patients with achalasia or SSc had normal bolus transit. Fifty-one percent of patients with IEM and 55% of patients with DES had normal bolus transit, whereas almost all patients with normal EM (95%), nutcracker esophagus (97%), poorly relaxing LES (100%), hypertensive LES (96%), and hypotensive LES (100%) had normal liquid bolus transit.

MMA

Twenty-four patients were diagnosed with MMA. Of these 24 patients, 9 patients had characteristics of achalasia and IEM, 7 with achalasia and DES, 3 with SSc and IEM, 2 with achalasia and SSc, 2 with DES and IEM, and 1 with nutcracker esophagus and DES.

IEM Demographics and Prevalence

One hundred and ten patients with IEM were assessed using HRIM. Of these patients, 80 (73%) were white and 74 (67%) were female. Of the 97 patients receiving both liquid and viscous swallows, 11 (11%) patients had mild IEM, that is, normal bolus transit for liquid and viscous, 24 (25%) patients had moderate IEM with either abnormal liquid or abnormal viscous bolus transit, and 62 (64%) patients had severe IEM with abnormal liquid and viscous bolus transit. The primary symptoms for which IEM patients were referred for esophageal function testing were diverse and included: dysphagia (13%), chronic cough (18%), chest pain/pressure (12%), heartburn (14%), regurgitation (15%), epigastric pain (8%), throat clearing (5%), asthma (4%), and other (12%).

DISCUSSION

The results of this study using the HRIM catheter with the newer conventional diagnostic criteria for IEM and the nutcracker esophagus update the prevalence of esophageal abnormalities previously reported from our laboratory 10 years ago.[6] Despite the advent of the Chicago Classification System, this study used the conventional diagnostic criteria to standardize data analysis with our previous study. In the past decade, the prevalence of normal manometry, achalasia, SSc esophagus, hypertensive LES, and hypotensive LES have remained the same. However, nutcracker esophagus, poorly relaxing LES, IEM, and DES show

TABLE 1. Demographic Parameters of all Patients

Diagnosis	Patients [n (%)]	Female Patients [n (%)]	Mean Age	Age Range	White [n (%)]	Black [n (%)]
Normal manometry	121 (35)	91 (76)	56	16-84	63 (72)	22 (25)
Achalasia	28 (8)	14 (50)	61	17-81	22 (79)	6 (21)
SSc	5 (1)	3 (60)	59	49-78	2 (40)	3 (60)
IEM	110 (31)	74 (67)	56	17-82	80 (73)	29 (26)
DES	9 (3)	4 (44)	68	40-83	9 (100)	0 (0)
Nutcracker	12 (3)	11 (92)	57	37-79	8 (67)	3 (25)
Hypertensive LES	26 (7)	18 (69)	59	30-79	19 (73)	5 (19)
Hypotensive LES	6 (2)	4 (67)	52	17-77	6 (100)	0 (0)
Poorly relaxing LES	9 (3)	4 (44)	55	23-75	5 (56)	3 (33)
MMA	24 (7)	12 (50)	62	30-83	16 (67)	7 (29)

DES indicates distal esophageal spasm; IEM, ineffective esophageal motility; LES, lower esophageal sphincter; MMA, major motility abnormality; SSc, scleroderma.

significant changes in prevalence. Likewise, MMA as a diagnostic category has emerged and accounts for 7% of diagnoses made from this laboratory.

The data show a decrease in the prevalence of the nutcracker esophagus from 9% ten years ago to 3% now ($P < 0.002$). This comes as no surprise as the manometric criteria for the diagnosis of nutcracker esophagus used in our laboratory became more stringent in the past 10 years from an average DEA > 180 mm Hg to an average DEA > 220 mm Hg for the 10 liquid swallows. However, it should be noted that of our 12 patients diagnosed with nutcracker esophagus, only 9 were diagnosed by conventional manometry standards. Three patients had DEAs slightly < 220 mm Hg, but met Chicago Classification version 2.0[7] high-resolution manometry requirements for nutcracker (mean DCI > 5000 mm Hg s cm). These observations suggest that perhaps the criteria for "hypercontractile esophagus" by HRIM have been set too low and are consistent with the most recent criterion suggested by the International Working Group[8] as well as a recent study from our laboratory.[9]

Likewise, the prevalence of poorly relaxing LES decreased from 9% to 3% ($P < 0.0001$). With the advent of high-resolution manometry catheters, the closely spaced pressure sensors provide a more complete and accurate assessment of the LES, which essentially eliminates errors because of sensor placement or LES movement. Consequently, we believe that 3% is a more accurate assessment of the prevalence of poorly relaxing LES; however, 22 of the 26 patients diagnosed with hypertensive LES had a poorly relaxing LES, which could account for the decrease in prevalence.

Surprisingly, we found an increase in the prevalence of IEM over the last decade (2004—IEM in 20% of patients, 2014—IEM in 31%; $P < 0.001$) despite the manometric criteria for IEM becoming more stringent, that is, requiring 5 of 10 instead of 3 of 10 contractions with an amplitude of < 30 mm Hg in the distal esophagus. One would have expected the prevalence to decrease in a similar manner as the nutcracker esophagus findings. In addition, in comparing the rates of mild, moderate, and severe IEM to a study from our laboratory done 5 years ago,[10] the prevalence of severe IEM has increased from 47% to 63% ($P < 0.01$) among patients found to have IEM. These findings suggest that there is an increase in the prevalence as well as the severity of IEM.

IEM is a frequent motility disorder in patients with gastroesophageal reflux disease (GERD)[11] and has been shown to increase in prevalence as the severity of reflux disease progresses from nonerosive reflux disease to erosive esophagitis to Barrett esophagus.[12] The most recent National Ambulatory Medical Care Survey documented that the rate of GERD-related doctor visits has nearly doubled from 1995 to 2006.[13] Although it remains unclear whether GERD is a cause of IEM or vice versa, it is tempting to consider that the 2 increases in prevalence may be related. Diabetes, specifically diabetic autonomic neuropathy, has also been associated with esophageal dysmotility, decreased amplitudes of contraction, and abnormal wave forms.[14,15] As diabetes has increased in prevalence, especially in older adults,[16] within the past decade, it is also another possible explanation for the increase in IEM prevalence.

Finally, the prevalence of DES has decreased from 9% to 3% ($P < 0.0001$), whereas neither the manometric criteria nor the technology have changed in making this diagnosis. Difficult to catch on manometry testing due to its sporadic and infrequent occurrence, DES is hard to diagnose and even harder to rule out of a differential. Furthermore, our laboratory has implemented "rule #1," by which we believe that it is better to underdiagnose than to overdiagnose motility abnormalities. Clinical experience suggests that the term distal esophageal spasm in particular can often cloud other diagnoses. Consequently, tracings that suggest DES are examined with additional care to confirm that every DES diagnosis is strong (ie, borderline cases are adjusted to normal). Finally, the addition of the MMA category has captured some of the prior DES diagnoses.

To compare bolus transit for liquid swallows to the earlier analysis completed 10 years ago, patients from the current study who had normal liquid impedance are shown in Figure 3. These results differ from the data gathered from our laboratory 10 years ago in 2 ways. First, the earlier study demonstrated that normal EM, nutcracker esophagus, poorly relaxing LES, hypertensive LES, and hypotensive LES all had normal bolus transit for liquid swallows in 95% of patients or greater. Although liquid bolus transit in nutcracker esophagus and hypotensive LES are not significantly different from 10 years ago, hypertensive LES, poorly relaxing LES, and normal manometry are all significantly different ($P < 0.002$). Consequently, this study's data do not support the conclusion made in our laboratory that esophageal body pressures are the main determinants of complete bolus transit. Instead, the data suggest that hypertensive LES and poorly relaxing LES can impair bolus transit in about half of patients. It has been known that when combined with an esophageal body dysfunction, the patients' symptoms stem primarily from the abnormality in LES relaxation and that inadequate LES relaxation causes delayed esophageal clearance.[3] As the majority of patients from this study who were grouped under hypertensive LES also had a poorly relaxing LES, further analysis is needed as to whether both LES abnormalities result in bolus transit delay.

Although the bolus transit for liquid swallows for patients with normal manometry is significantly different compared with 10 years ago, we believe this is skewed by the effects of GERD. A recent study by Savarino et al[12] found that some patients with severe reflux disease presented with normal manometry and abnormal bolus transit. As 13 of the 18 (72%) patients with abnormal bolus transit for liquid swallows and normal manometry had abnormal reflux studies completed in our laboratory as well, we feel that this supports Savarino and colleague's study and deserves future analysis.

Secondly, the prior study showed that half of patients with IEM (51%) had normal bolus transit for liquids. We believe the drastic decrease in this number to 15% ($P < 0.0001$) is indicative of both the change in the IEM definition and the rise in prevalence of severe IEM. In addition, normal bolus transit for liquids in patients with DES dropped from 55% ten years ago to 0% in the current study ($P < 0.01$). Consequently, we believe that the manometric parameters and patterns do not overestimate the functional defect caused by IEM and DES.

This study is limited by the lack of comparison of the HRIM to barium studies that could have possibly confirmed or clarified the diagnosis for many of the patients categorized as MMA. Therefore, we cannot comment on the diagnostic accuracy and advantages of MMA as a diagnostic term. Further analysis of these findings is the focus of a subsequent study from our laboratory. In addition, one could regard the use of conventional manometry criteria as a further limitation arguing that we missed out on the chance to use the Chicago classification with the HRIM recordings. As the study published 10 years ago used the conventional Spechler-Castell classification system, we considered it more appropriate to use the same system when evaluating changes in prevalence of manometric findings over time.

In summary, although most of the "named" esophageal motility disorders have not changed in prevalence or have fluctuated in a predictable manner, IEM has significantly increased in prevalence and severity. Further studies are needed to evaluate possible causes for this and to better clarify the IEM, GERD, and diabetes relationship. A suggestion is made in support for a new small subclass of MMA, which we feel has been helpful in our laboratory to identify the occasional poorly defined but definitely abnormal study. The findings of this investigation also suggest that a change in the classification of esophageal motility abnormalities which better blends the manometry and bolus transit may be needed. Further analysis of the dynamics of the LES in relation to esophageal functional defects likely defined by HRIM is also needed.

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