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Manometric Subtypes of Ineffective Esophageal Motility

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OBJECTIVES: Ineffective esophageal motility (IEM) is characterized by well-defined manometric criteria. However, much variation exists within the diagnosis: Some patients exhibit exactly the required five weak swallows to make the diagnosis. Others show consistently ineffective swallows with total absence of any normal swallow. "We hypothesize" there are two different manometric subtypes of IEM; IEM Alternans (IEM-A) and IEM Persistens (IEM-P).

METHODS: A total of 231 IEM patients were identified by high-resolution manometry (HRM). IEM defined by distal contractile integral (DCI) <450 mm Hg/s/cm in $\geq 50\%$ of test swallows. Abnormal reflux study was defined by excess total number of reflux episodes, abnormal esophageal acid exposure, or positive symptom association.

RESULTS: A total of 195 (84%) patients had IEM-A and 36 (16%) had IEM-P. A striking gender difference with 34% of IEM-A being males compared to 53% of IEM-P. ($P=0.03$). Mean age of IEM-P (59.6 years+/−13.1) was greater than IEM-A (55.5 years+/−13.6) ($P=0.04$). Mean lower esophageal sphincter (LES) resting pressure was significantly lower in IEM-P (20.8 mm Hg+/−1.4) than IEM-A (29 mm Hg+/−1.2) ($P=0.002$). There was no difference in LES-integrated relaxation pressure (IRP), bolus transit, or manometric presence of hiatal hernia between the two groups. Out of 146, 89 (61%) patients had abnormal reflux study. Esophageal acid exposure in upright position was significantly higher in IEM-P than IEM-A (3.5 vs. 1.7%, $P=0.04$). Poor gastric acid control on proton pump inhibitor (PPI) was more prevalent among IEM-P patients (58%) than IEM-A (27%) ($P=0.007$). In subgroup analysis of 41 IEM patients with dysphagia, DCI for liquid swallows was significantly lower in IEM-P (111+/−142 mm Hg/s/cm) compared to IEM-A (421+/−502 mm Hg/s/cm) ($P=0.04$), lower mean LES resting pressure in IEM-P (16.6+/−9 mm Hg) than IEM-A (31.7+/−18 mm Hg) ($P=0.01$).

CONCLUSIONS: There are two distinct manometric IEM subtypes; IEM-P with an older male predominance, more advanced reflux disease, weaker LES, and worse response to PPI; likely a more advanced manifestation than IEM-A. However, the question if there are different etiologies underlying the two subtypes remains to be answered.

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INTRODUCTION

Ineffective esophageal motility (IEM) is identified by a well-defined set of manometric criteria[1] but its etiology is poorly understood. It was initially defined in 1997 by Leite *et al.*,[2] its definition and nomenclature were standardized by Spechler and Castell,[3] and subsequently revised.[4] IEM is the most common abnormal manometric finding in our esophageal laboratory (20–30%).[5] Current guidelines of diagnosis require low amplitude pressures (distal contractile integral (DCI) <450 mm Hg/s/cm on high-resolution manometry (HRM)) in $\geq 50\%$ of test swallows.[1,5,6] Defective bolus transit (DBT), as noted on impedance measurement ($>20\%$ of liquid swallows and/or $>30\%$ of viscous swallows), is used to attach the adjectives "mild" (normal BT for liquid & viscous swallows), "moderate" (DBT for either liquid or viscous swallows), or "severe" (DBT for both liquid & viscous swallows) to the diagnosis.[4] Its pathophysiology and clinical significance are still being debated. There is much suggestion in the literature that IEM is associated with coexisting gastroesophageal reflux disease (GERD), but causality or interaction of the two conditions still remains unknown.[2,7–14] On the other hand, there are studies that show different results even though their data do not disprove some association between GERD and IEM, but rather declare that IEM is not standing alone as a cause of GERD.[15–17] Other hypotheses suggest an association with rapid food intake,[18,19] Vagal hyper-reactivity,[20] advanced age,[21,22] or damage to the enteric nervous system or smooth muscle[16] as possible etiologies. Furthermore, patient demographics such as age, sex, and race of afflicted patients are subjects of debate.[21–23]

While the manometric diagnosis of IEM is made when $\geq 50\%$ of test swallows are noted to be weak, variation exists within the diagnosis. Within the 10 usually analyzed liquid test swallows, some patients will show exactly five low amplitude swallows, but also exhibit some normal swallows in between—this is known locally within our laboratory as "IEM Alternans" or IEM-A (Figure 1). Other patients reveal consistently low amplitude swallows with no single normal swallow seen; this subtype is named "IEM Persistens" or IEM-P in our laboratory (Figure 2).

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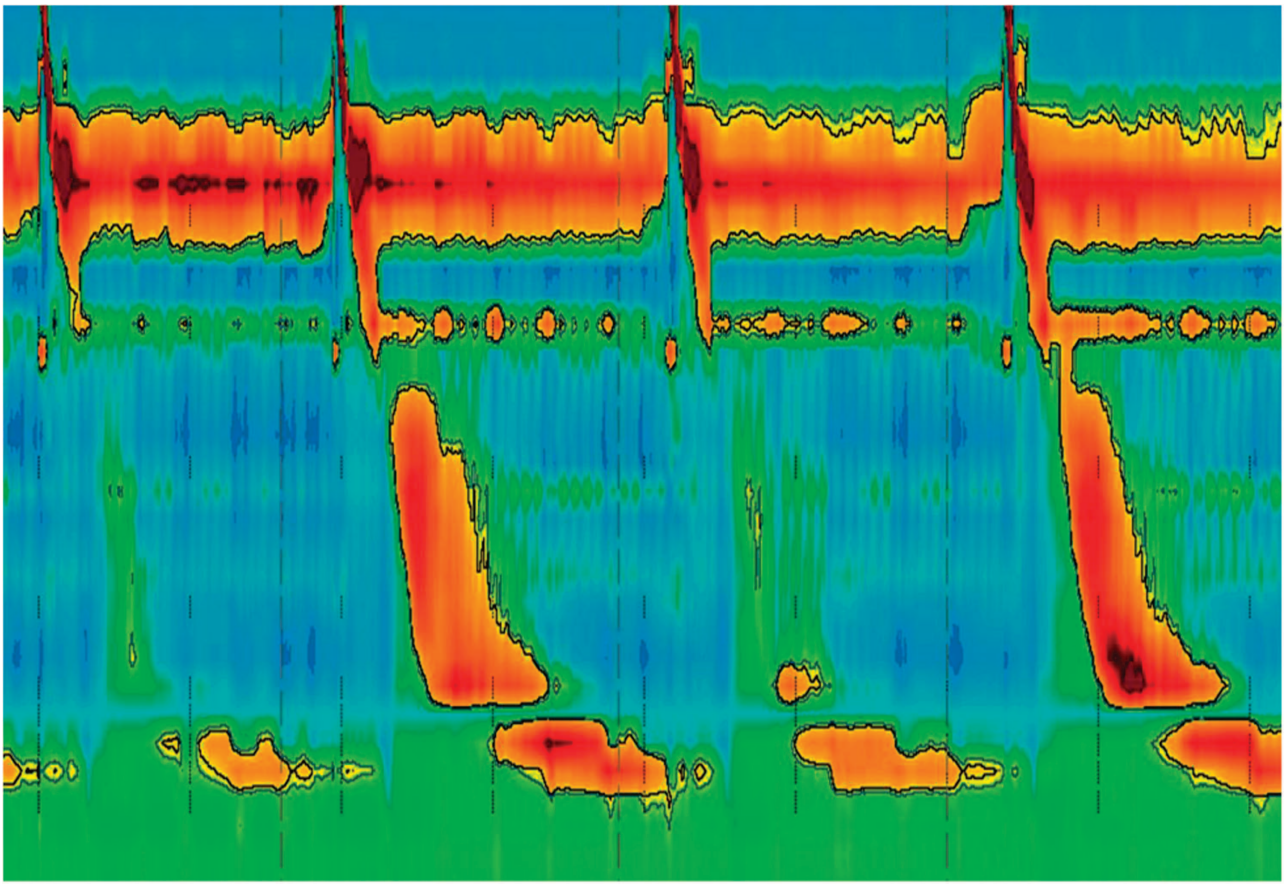

Figure 1 High-resolution manometry pressure topography showing a section (4 swallows) of "IEM- Alternans": Ineffective swallows alternating with normal swallows.

The goal of this study was to more closely investigate these two different subtypes concerning patients' demographics, presenting symptoms, manometric, and impedance metrics and association with pathological GERD. We proposed that either "IEM Persistens" is a more advanced manifestation of "IEM Alternans" with the same underlying etiology or that the two are different disorders with heterogeneous pathophysiology.[15,16]

METHODS

Patients. We searched retrospectively the database of the Medical University of South Carolina (MUSC) Esophageal Motility Laboratory from 7/2010 to 8/2013 for IEM patients according to HRM criteria (DCI $<$ 450 mm Hg/s/cm in $\geq$ 50% of test swallows). A total of 962 tracings performed with a combined high-resolution impedance manometry (HRIM) system were reviewed, 231 (24%) of those were diagnosed as IEM. Of the 231, 146 patients had reflux monitoring study performed as ordered by referring physician for concerns of pathological GERD.

Combined impedance-manometry and impedance-pH monitoring. The UNI-ESO-WG1A1 High-Resolution Probe (Sandhill Scientific Inc., Highlands Ranch, CO, USA) is a 4-mm diameter catheter with 32 circumferential pressure channels and 16 impedance channels. The data collected with the high-resolution impedance manometry (HRIM) probe can be displayed in color-coded pressure topography plots.[24]

The multichannel intraluminal impedance-pH (MII-pH) catheter is a 2.1-mm-diameter polyurethane catheter incorporating 6 impedance segments and two pH-measuring antimony electrodes located 5 cm above the LES and at 10 cm below the LES in the gastric fundus[25] (Sandhill Scientific).

Study protocol. All study participants presented to the esophageal laboratory with various complaints (dysphagia, chest pain, cough, throat clearing, hoarseness, regurgitation, heartburn, epigastric pain, or other complaints), who had no esophagitis on upper endoscopy and no previous history of esophageal or gastric surgery, were evaluated with a combined HRIM for the purpose of guiding their ongoing clinical treatment.

Subjects underwent HRIM testing with 10 liquid (5 ml normal saline) swallows performed 30 seconds apart, and patients refrained from swallowing in between test swallows. This was followed by 10 viscous (5 ml of applesauce-like substance) swallows. Subsequently, the data were analyzed with the Sandhill BioVIEW Analysis Suite 64 software (Sandhill Scientific Inc.).[24]

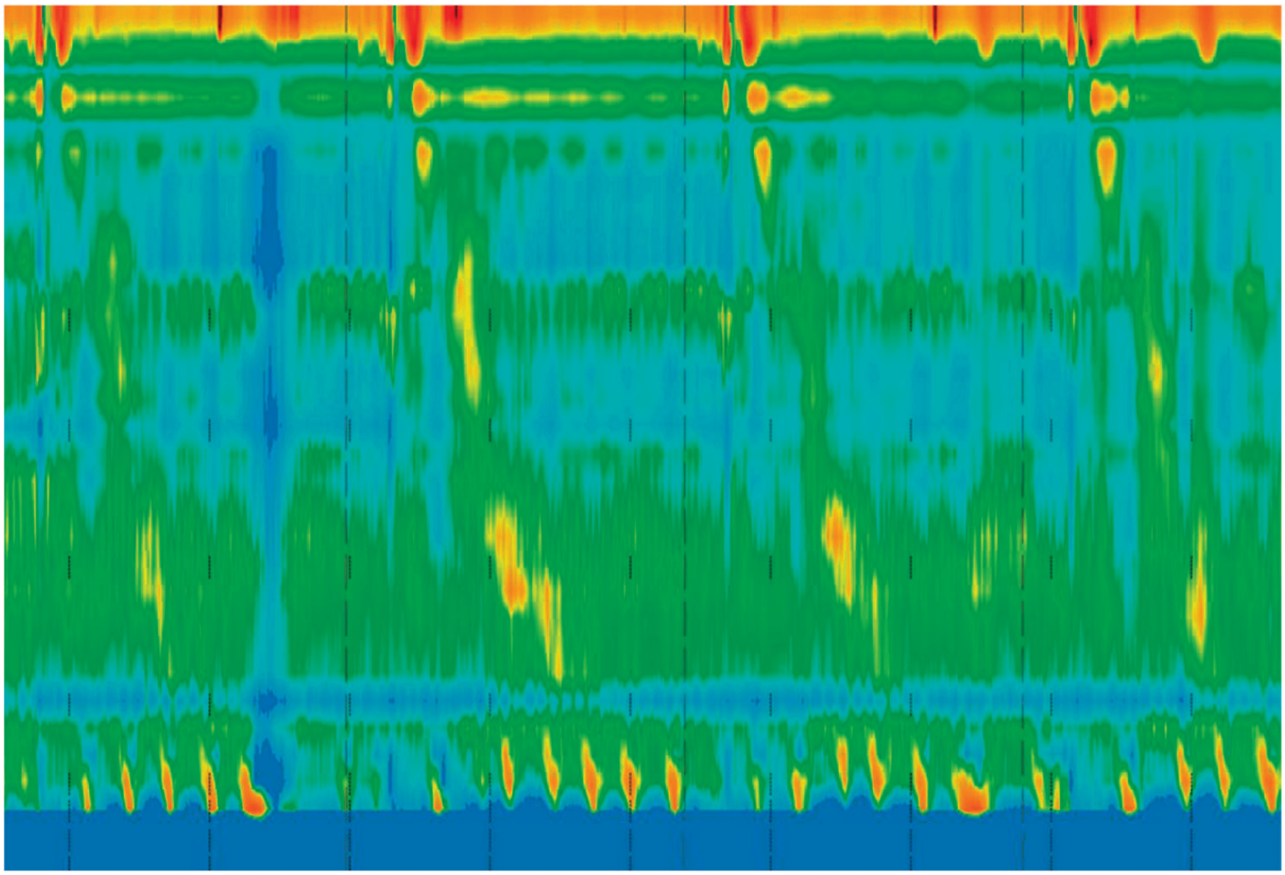

Figure 2 High-resolution manometry pressure topography showing a section (4 swallows) of "IEM- Persistens": Ineffective swallows with no single normal swallow seen out of 10 test swallows.

After completion of the combined HRIM study, patients underwent ambulatory combined MII-pH testing, if they presented with symptoms concerning for pathological GERD (146/231 patients). Testing was done while patients were on treatment with proton pump inhibitor (PPI) in 84% of the patients, and off PPI in 16%. All events during testing, including meals, medications, symptoms, and body position (upright/recumbent), were entered by the patient directly into the monitor. The patient was also asked to keep a diary of activities during testing. Participants had ambulatory monitoring done for a minimum of 16 h.

Approval for performing this study and publishing information was obtained from the Institutional Review Board (IRB) of the Medical University of South Carolina (MUSC).

Data analysis. Demographic, clinical characteristics, and symptom distribution of patients were analyzed for IEM-A and IEM-P patients. The definition of IEM according to both High-Resolution Manometry and Conventional Line Tracings requires that only 5 out of 10 study swallows show low amplitude or DCI. This allows for a range of weak swallows (that is, 1–4) to be "normal" and also to be weak (5–10). It is our clinical perception that the latter might represent a more advanced form of IEM.

Bolus transit for liquid and viscous swallows, and mean resting LES pressure were compared between the two groups.

Subgroup analysis of IEM-A and IEM-P patients who presented with dysphagia included distal contractile integral (DCI), integrated relaxation pressure (IRP), mean resting LES pressure, and bolus transit data for liquid and viscous swallows.

Parameters calculated from the combined MII-pH monitoring included: Gastric acid control on PPI; distal esophageal acid exposure (that is, time with esophageal pH <4 in upright and recumbent positions); total number of reflux episodes, and symptom index for the three most prominent symptoms.[19,26,27]

The level of gastric acid control for each impedance-pH study was performed by a direct visual inspection of the 24-h gastric pH study using the following score:

Excellent: gastric pH above 4 throughout the study, both upright and recumbent.
Good: gastric pH >4 most of the study except for occasional pH level <4 while recumbent. This is consistent with pharmacologic nocturnal acid breakthrough.
Fair: frequent decreases of gastric pH <4, both upright or recumbent.
Poor: gastric pH <4 most of the 24 h (looks similar to patient not taking medications).

Table 1 Demographic and clinical characteristics of IEM-P and IEM-A showing an older male predominance of IEM-P

IEM patients (231)	IEM-P (195)	IEM-A (36)	*P*-value
Age (average in years) +/ – s.d.	59.6 +/ – 13.1	55.5 +/ – 13.6	***0.047***
Sex (males)	53%	34%	***0.035***
Race (white)	75%	71%	0.84
BMI, kg/m^2+/ – s.d.	30.1+/ – 7.7	29.1+/ – 4.2	0.22
Diabetes mellitus	21%	13%	0.22
Alcohol abuse	28%	33%	0.80
Tobacco use	41%	39%	0.58
Connective tissue disease	14%	6%	0.82
Neurological disease	0%	1%	0.67

BMI, body mass index; IEM, ineffective esophageal motility; IEM-A, IEM-alternans; IEM-P, IEM-persistens.
Bold and italic values signify the significant results.

As published by our group in 2012, there was a strong correlation ($r=0.9$) between the qualitative scale of acid control and the numerical value for percentage of time that the gastric pH was >4.[28]

Pathological GERD was defined on MII-pH study by the following criteria: Excess total number of reflux episodes ($\geq$48 episodes/24 h on or off PPI); abnormal esophageal acid exposure ($\geq$6.3% in upright position and/or $\geq$1.2% in recumbent position off PPI, or $\geq$1.5% in upright position and/or $\geq$0.5% on PPI); or positive symptom association (symptom index $\geq$50%).[29]

Statistical analysis. Descriptive statistics (mean, s.d.) were used to evaluate demographic and manometric findings in the two groups of IEM patients. The data were maintained on an Excel (Microsoft, MUSC) spreadsheet at Medical University of South Carolina and analyzed using the unpaired *t*-test for normally distributed continuous parameters. χ^2/Fisher's exact tests were used to assess differences in proportions of patients/measurements. *P*-value <0.05 was used to indicate statistical significance.

RESULTS

A total of 195 (84%) patients with IEM-A and 36 (16%) with IEM-P were identified. There was a striking gender difference with 128 (66%) females and 67 (34%) males having IEM-A vs. 17 (47%) females and 19 (53%) males with IEM-P ($P=0.035$). The mean age of IEM-P patients (59.6 years+/ – 13.1) was significantly higher than that of IEM-A (55.5 years+/ – 13.6) ($P=0.04$). There was no significant difference in race: 139 (71%) whites, 52 (27%) blacks in IEM-A vs. 27 (75%) whites and 9 (25%) blacks in IEM-P ($P=0.84$). There was no significant difference between the two groups in the following variables: body mass index (BMI), diabetes mellitus, tobacco use, alcohol use, connective tissue disease, or neurologic disease (Table 1).

Symptom distribution of the main presenting symptom at time of manometry study in all IEM patients is depicted in Figure 3. Dysphagia was the main presenting symptom in 18%, followed by cough (15%), chest pain (13%), regurgitation (12%) and heartburn (12%).

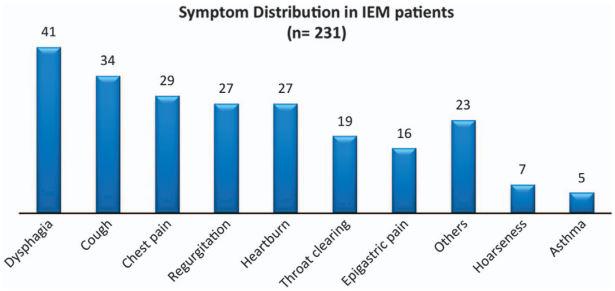

Figure 3 Symptom distribution in IEM patients (231). Dysphagia is the main presenting symptom. IEM. Ineffective esophageal motility.

Table 2 Main presenting symptoms for IEM-P and IEM-A

Main presenting symptom	IEM-P	IEM-A	*P*-value
Dysphagia	22%	17%	0.44
Chest pain	17%	12%	0.41
Heartburn	6%	13%	0.21
Cough	8%	16%	0.1
Throat clearing	3%	9%	0.2
Hoarseness	0%	4%	0.25
Epigastric pain	6%	7%	0.72
Regurgitation	11%	12%	0.9

IEM-A, IEM-alternans; IEM-P, IEM-persistens.

Although dysphagia and chest pain were more prevalent in IEM-P and heartburn, regurgitation, cough and throat clearing were more prevalent in IEM-A patients, that did not reach significance level (Table 2).

In 226 out of 231 patients, the LES was interpretable. The mean resting pressure was significantly lower in IEM-P (20.8 +/ – 1.4 mm Hg), compared to IEM-A (29+/ – 1.2 mm Hg) ($P=0.002$). There was no significant difference in LES-integrated relaxation pressure (IRP), or manometric presence of hiatal hernia between the two groups. Defective bolus transit (DBT) for both liquid and viscous swallows was present in 21/36 (58%) of IEM-P vs. 120/195 (62%) of IEM-A, ($P=0.71$).

In subgroup analysis (Table 3), 41 patients had dysphagia as main presenting complaint, of which 33 had IEM-A (17% of IEM-A patients) and 8 had IEM-P (22% of IEM-P patients) ($P=0.27$). Mean DCI for liquid swallows was significantly lower in IEM-P (111+/ – 142 mm Hg/s/cm) compared to IEM-A (421+/ – 502 mm Hg/s/cm) ($P=0.047$). Mean LES resting pressure among dysphagia patients was significantly lower in IEM-P (16.6+/ – 9 mm Hg) compared to IEM-A (31.7 +/ – 18 mm Hg) ($P=0.01$).

Out of 231, 146 patients had an ambulatory reflux study done as ordered by the referring physician for evaluation of clinical symptoms suspected to be secondary to pathologic reflux disease. 84% of reflux studies were done on PPI. Out of 146, 89 reflux studies (61%) were abnormal. Of the 89 abnormal reflux studies, 76 were IEM-A (85%) and 13 IEM-P (15%) ($P=0.13$). The average percentage of esophageal acid exposure in the upright position was significantly higher in IEM-P than IEM-A (3.5 vs. 1.7%, $P=0.04$). Poor gastric acid control (pH <4 most of the 24 h of the pH study (looks similar to patient not taking medications)) was significantly more

Table 3 Manometric characteristics between IEM-P and IEM-A patients who presented with dysphagia as main symptom

IEM Patients with dysphagia $N=41$ (%)	IEM-P 8 (22%)	IEM-A 33 (17%)	*P*-value
Average DCI for liquid swallows (mm Hg/s/cm)+/ – s.d.	111+/ – 142	421+/ – 502	***0.047***
Average DCI for viscous swallows (mm Hg/s/cm)+/ – s.d.	145+/ – 142	468+/ – 354	0.058
Mean LES resting pressure (mm Hg)	16.6+/ – 9	31.7+/ – 18	***0.01***
IRP (integrated relaxation pressure) (mm Hg)	15+/ – 2.1	23.1+/ – 16.2	0.27
Defective bolus transit for liquid swallows	85%	89%	0.27
Defective bolus transit for viscous swallows	95%	83%	0.1

IEM, ineffective esophageal motility; IEM-A, IEM-alternans; IEM-P, IEM-persistens.
Bold and italic values signify the significant results.

Table 4 Reflux characteristics of IEM-P and IEM-A patients showing more esophageal acid exposure in upright position and poor gastric acid control in IEM-P patients compared to IEM-A patients

IEM Patients, $N=231$ (%)	IEM-P, 36 (16%)	IEM-A, 195 (84%)	*P*-value
Abnormal reflux study	13/17 (76%)	76/129 (59%)	0.13
Hiatal hernia	6/36 (17%)	32/195 (17%)	1
Upright esophageal acid exposure	3.5%	1.7%	***0.04***
Recumbent esophageal acid exposure	1.6%	1.0%	0.59
Positive symptom association (SI $\geq$ 50%)	7 (41%)	60 (47%)	0.8
Number reflux episodes/24 h	40	44	0.69
Gastric acid control on PPI			
Excellent	2 (12%)	19 (18%)	0.55
Good	4 (24%)	30 (27%)	0.73
Fair	1 (6%)	31 (28%)	0.05
Poor	10 (58%)	29 (27%)	***0.007***

IEM, ineffective esophageal motility; IEM-A, IEM-alternans; IEM-P, IEM-persistens; PPI, proton pump inhibitor; SI, symptom index.
Bold and italic values signify the significant results.

prevalent in IEM-P (58%) than in IEM-A (27%) ($P=0.007$). There was no significant difference in symptom association with reflux disease (Symptom Index (SI) $\geq$ 50%) between IEM-A and IEM-P groups (SI = 47% for IEM-A and 41% for IEM-P) ($P=0.80$). Detailed analysis of reflux studies for IEM-P and IEM-A patients is summarized in Table 4.

DISCUSSION

Ineffective esophageal motility (IEM) is the most common motility abnormality found in our esophageal function laboratory. Characterized by low amplitude peristalsis in the distal esophagus,[1,3,6] it is often associated with impaired bolus transit.[30,31] Nevertheless, the clinical significance and pathophysiology of this disorder is still open to debate.

Using the Chicago Classification criteria[1,6,32] as a model, the aim of this study was to more closely investigate two manometric patterns of IEM; "IEM Persistens" (IEM-P) without any single normal swallow seen vs. "IEM Alternans" (IEM-A) with normal swallows seen in between the five or more weak ones. Our results show an older male predominance of IEM-P with more acid exposure in upright position, weaker LES and poor response to acid suppression, which seems consistent with more advanced reflux disease. To date, the majority of studies in this field suggest an important role of IEM in increased esophageal acid exposure. Several studies have repeatedly shown that esophageal hypomotility is increasingly prevalent with increasing severity of GERD.[2,13,33,34] Additionally, a functional defect in the esophagus with impaired acid clearance has been suggested to be related to IEM.[30,35] Inspite of that, it has not been shown whether IEM is a primary motor abnormality or a secondary motility disorder due to chronic inflammation. There are experimental studies that report reversibility of esophageal hypomotility after healing of inflammation.[36–38] Fornari and colleagues reported a transient reversibility of over 50% in 11 patients with severe IEM after adequate cholinergic stimulation of the esophagus.[34] However, other studies show that patients with chronic erosive GERD did not recover from esophageal dysmotility after pharmacological or surgical treatment of their reflux disease.[39–41] This controversy could be explained possibly by a dysfunctional neuromuscular control due to inflammatory mediators in acute GERD-related esophagitis vs. fibrosis in chronic inflammation. To date, there is evidence in the literature for both neurological and myopathic pathologies underlying IEM.

Kim and colleagues had a closer look at the histopathologic abnormalities of esophageal neuromuscular structures in esophageal tissues of patients with total gastrectomy due to gastric cancer. They reported that esophageal smooth muscle of patients with IEM frequently exhibited fibrosis, myolysis and widened intercellular spaces, suggesting the possibility of a myopathic process. In addition, more neuronal nitric oxide synthase (nNOS) immunoreactivity was seen in the circular muscle layer of patients with IEM, thus excess nitric oxide (NO) production with consecutive diminished amplitude of esophageal peristalsis is one plausible mechanism for IEM. The esophageal tissues revealed histopathologic changes of myopathy, whereas the myenteric plexus appeared morphologically normal, another indication that the myopathic process may contribute more to pathogenesis of IEM.[16]

In contrast to the myopathic etiology of IEM, there are several studies that suggest a relationship between esophageal dysfunction and neuropathy like in some patients with diabetes mellitus,[42–44] where acute hyperglycemia is believed to be an unlikely contributing factor.[45,46] However, there is evidence that neurologic factors play a role in the pathophysiology of esophageal dysmotility. Stewart and colleagues documented that 31 diabetic patients with autonomic neuropathy revealed diminished peristaltic amplitudes and esophageal emptying as well as a reduced LES pressure.[47] Because the patients were suffering from diabetic neuropathy, the degeneration of the ganglion cells of the esophageal myenteric plexus was assumed to be associated with hypersensitivity of the esophageal smooth muscle to cholinergic agents. In fact, bethanechol, a cholinergic drug with muscarinic actions, accelerated esophageal emptying and increased the LES resting pressure.[48] The group concluded that, in diabetic autonomic neuropathy, the predominant lesion is in the preganglionic fibers of the vagus rather than in the myenteric plexus of the esophageal wall. In addition, Hollis and colleagues stimulated the esophagus of 50 patients with diabetes mellitus and healthy subjects with edrophonium, an effective acetyl-cholinesterase inhibitor. There was a significant decrease in peristaltic velocity in diabetics with peripheral neuropathy when compared to diabetics without neuropathy and controls. It was concluded that abnormal motility in diabetes mellitus was associated with peripheral neuropathy and was characterized by a dysfunction of esophageal innervation with intact smooth muscle function.[49] Although our study showed a profoundly weaker LES and pronounced reflux in IEM-P compared to IEM-A patients, diabetes mellitus was not significantly different between our two groups. A possible explanation of such finding could be related to the high prevalence of diabetes in the patient population as a whole (18%), same as BMI (average 29.3 kg/m^2).

Dysphagia was the most prevalent symptom among patients with IEM (18%). Subgroup analysis of IEM patients with dysphagia, as a severe symptom of esophageal dysmotility, showed a drastically weaker LES and much lower DCI for liquid swallows in IEM-P compared to IEM-A, affirming our hypothesis of a manometric gradient between the two groups.

Bolus transit (BT), a measure of esophageal function depicted non-invasively by impedance measurement, was very defective in both IEM-P (85% of liquid and 95% of viscous swallows) and IEM-A (89% of liquid & 83% viscous swallows) patients who presented with dysphagia, without significant difference between the two groups. BT was also noticeably defective for both liquid and viscous swallows in the whole group of IEM patients (58% for IEM-P and 62% for IEM-A). These important findings of severely defective bolus transit (DBT) in IEM patients, although not significantly different between the two groups, indicate that IEM carries an important functional defect that manifests in different array of symptoms and could have an adverse implication on the patient.

There are limitations in our present study. The retrospective nature of the analysis involves lack of detailed medical data of all included patients as the operator could only rely on the available documented data. As many patients get referred to our open-access esophageal motility laboratory for the manometric and reflux-monitoring studies while they receive medical care by the referring physician, concluding outcome data would be a challenging task. A more prospective analysis of IEM subtypes could elaborate more on this important aspect. Furthermore, our study has not been blinded. However, it is extremely difficult to incorporate bias in the data analysis of the measured metrics that has already been analyzed and interpreted.

In summary, our results support the concept of two manometric subtypes of IEM and suggest an association between IEM and GERD, with IEM-P showing a significantly higher esophageal acid exposure in upright position along with worse response to acid suppression therapy than IEM-A. Furthermore, IEM-P shows an older male predominance, which might be indicative of chronic reflux disease. In addition, LES tone was weaker in IEM-P. However, we doubt that GERD is standing alone in the etiology of IEM, although an association with diabetes, connective tissue disease or neurological disorder could not be shown in our study. Further studies are needed to shed more light on this controversial complex issue.

CONFLICT OF INTEREST

Guarantor of the article: Donald O. Castell, MD, MACG.
Specific author contributions: Hiestand: collected the initial data, performed initial analysis, and drafted initial manuscript. Abdel Jalil: Further data collection and critical data analysis, drafted the manuscript and its subsequent revisions. Submitted manuscript to the journal. Castell: concept/design of the study. Critical revision and approval of manuscript, and subsequent revisions. All authors have approved the final draft submitted.
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Potential competing interests: None.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Ineffective esophageal motility (IEM) is the most common esophageal motility abnormality.
- ✓ IEM is diagnosed when $\geq$ 50% of test swallows are weak (DCI $<$ 450 mm Hg/s/cm on high-resolution manometry).
- ✓ Gastroesophageal reflux disease (GERD) is prevalent in IEM patients.

WHAT IS NEW HERE

- ✓ Two distinct manometric subtypes of IEM exist: IEM-persistence (IEM-P) where all swallows are weak, and IEM-alternans (IEM-A) where normal and weak swallows alternate.
- ✓ IEM-P is associated with more advanced reflux disease, weaker lower esophageal sphincter (LES) and esophageal peristalsis and worse response to acid-suppression therapy, representing a more advanced disease than IEM-A.
- ✓ Older men tend to have more advanced IEM disease (IEM-P).

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