Ineffective Esophageal Motility (IEM): the Old-New Frontier in Esophagology

Ala’ A. Abdel Jalil¹ · Donald O. Castell²

Abstract Ineffective esophageal motility (IEM) is characterized by distal esophageal contraction amplitude of <30 mmHg on conventional manometry (Blonski et al. Am J Gastroenterol. 103(3):699–704, 2008), or a distal contractile integral (DCI)<450 mmHg*s*cm on high-resolution manometry (HRM) (Kahrilas et al. Neurogastroenterol Motil. 27(2):160–74, 2015) in ≥50 % of test swallows. IEM is the most common abnormality on esophageal manometry, with an estimated prevalence of 20-30 % (Tutuian and Castell Am J Gastroenterol. 99(6):1011–9, 2004; Conchillo et al. Am J Gastroenterol. 100(12):2624–32, 2005). Non-obstructive dysphagia has been considered to be frequently associated with severe esophageal peristaltic dysfunction. Defective bolus transit (DBT) on multichannel intraluminal impedance testing was found in more than half of IEM patients who presented with dysphagia (Tutuian and Castell Am J Gastroenterol. 99(6):1011–9, 2004), highlighting the functional defect of this manometric finding. Treatment of IEM has been challenging because of lack of promotility agents that have a definite effect on esophageal function.

Keywords Ineffective esophageal motility (IEM) · Dysphagia · Manometry · Impedance · Gastroesophageal reflux disease (GERD)

Introduction

Esophageal motility has two components: peristaltic pressure measured by manometry, and bolus transit measured by barium X-ray, radioisotopes, or intraluminal impedance. An esophageal motility abnormality can have a defect in either modality or both. Achalasia and esophageal involvement in scleroderma represent true esophageal motility disorders having a well-established pathology, whereas other abnormal motility patterns found in patients with chest pain, dysphagia, and heartburn have unclear clinical significance. The task at hand is to determine whether the distinct esophageal dysmotility categories truly matter in clinical practice [1].

IEM Is a Specific Motility Abnormality

Based on a study of esophageal pressure patterns in 95 healthy volunteers, Richter and Castell defined nonspecific esophageal motility disorder (NEMD) as ≥30 % of wet swallows with any combination of non-transmitted (failed) swallows and low-amplitude contractions (<30 mmHg) or at least one of the following contraction abnormalities: triple-peaked contraction, retrograde contraction, prolonged peristalsis (>6 s), or isolated incomplete lower esophageal sphincter (LES) relaxation [2]. NEMD was actually a vague category that included different phenotypes of poorly defined esophageal contraction abnormalities. Concurrent use of video fluoroscopy and manometry showed that esophageal hypomotility, in the form of hypotensive or failed peristalsis, has both functional and clinical relevance,
where contractions with amplitude < 30 mmHg were associated with ineffective bolus movement [3]. Leite et al. found 98% (60/61) of NEMD patients had ineffective esophageal motility (IEM), defined then by at least 30% ineffective contractures out of 10 test swallows. They proposed that IEM is a more appropriate term and should replace NEMD, giving it a more specific manometric identity [4•].

**Definition**

IEM was initially defined as ≥30% wet swallows showing ineffective peristalsis (<30 mmHg) at either distal site of esophagus (3 and 8 cm above LES) on conventional manometry [2, 3, 4•]. In 2001, using conventional manometry, Spechler and Castell defined IEM as distal esophageal hypocontractility in ≥30% of wet swallows, characterized either as contraction amplitude < 30 mmHg in the distal esophagus, 3 and 8 cm above the LES, or as peristaltic waves that are not propagated to the distal esophagus or absent peristalsis [5].

Tutuian and Castell indicated in 2004 that patients with ≥50% ineffective wet swallows (<30 mmHg) are more likely to have abnormal bolus transit [6], and that has been adopted as a new threshold for IEM manometric diagnosis in 2008 by Blonski et al., where they found that IEM with 50% or more ineffective wet swallows was more frequently associated with esophageal symptoms (dysphagia and heartburn) and abnormal bolus transit compared to those who had only 30–49% ineffective swallows [7••].

High-resolution manometry (HRM) is a new technology that utilizes up to 36 closely spaced sensors every 1 cm to measure esophageal intraluminal pressure during swallowing. This technique allows for a seamless, dynamic representation of the pressure pattern throughout the entire esophagus, thus obtaining information regarding anatomy and pressure gradients, along with the contractile activity [8].

The Chicago Classification (CC) categorizes esophageal motility disorders on HRM depicted with color pressure topography plots (Clouse plots). Although CC removed IEM from the classification scheme initially in an attempt to further subdivide hypomotility disorders (frequent failed peristalsis, weak peristalsis with large breaks, and weak peristalsis with small breaks), but then realized that this only added complexity and confusion, with unclear clinical significance. In its latest iteration, CC v 3.0 reintroduced the term of IEM, where it defines ineffective swallows by a distal contractile integral (DCI) of ≤450 mmHg·cm·sec, with ≥50% ineffective swallows constituting IEM. No distinction was made between weak swallows (DCI > 100 but ≤450 mmHg·cm·sec) and failed swallows (DCI < 100 mmHg·cm·sec) [9••, 10]. Figure 1 shows ineffective swallows on HRM in a patient with severe IEM.

**Primary or Secondary Abnormality?**

Gastroesophageal reflux disease (GERD) has been found to be prevalent in half of patients diagnosed with IEM on manometry, with Barrett’s esophagus patients having a strong predilection for this abnormality [11]. In addition, IEM has been noted as a frequent esophageal dysmotility in patients with diabetes mellitus, especially with concomitant autonomic dysfunction [12, 13]. Extensive esophageal endoscopic submucosal dissection (ESD) may cause esophageal dysmotility in some patients and might result in dysphagia [14]. Table 1 lists conditions where IEM may be found on esophageal manometry [11–14].

**Evaluation**

Esophageal manometry, by recording intraluminal pressure, is the gold standard to diagnose esophageal motility abnormalities [15, 16]. Application of multichannel intraluminal impedance (MII) monitoring in conjunction with manometry leads to improved diagnosis [17].

The unifying feature of swallows contributing to the diagnosis of IEM is poor bolus transit in the distal esophagus [9••]. The application of combined impedance-manometry technology provides relevant additional data regarding esophageal motility compared to manometry alone, particularly to identify abnormal bolus transport and clearance during swallows, and to investigate the relationships between bolus transit and LES relaxation [18].

In a study of 70 patients using combined impedance-manometry testing, factors controlling bolus transit in IEM patients were found to be low amplitude of esophageal contractions (<25 mmHg) and the number of swallows with low amplitudes (≥5). Two thirds of patients had abnormal bolus transit to saline swallows, viscous swallows, or both (17, 14, and 36%, respectively) [6].

**Symptom Distribution**

Analysis of 228 IEM patients who have been referred to our esophageal motility center at Medical University of South Carolina between 2010–2013 showed a predominance of dysphagia as the main presenting symptom (25% of patients), compared to cough (15%), chest pain (13%), heartburn (12%), regurgitation (12%), and various other symptoms (Fig. 2). Among patients with dysphagia, bolus transit was defective in 89% (30% to either saline or viscous swallows and 59% to both types of swallows). This predominance of dysphagia, along with defective bolus transit in patients with severe IEM was demonstrated back in 2008 [7••], underscoring that functional and clinical significance of IEM has not changed over time, despite differences in diagnostic criteria with HRM [7••].
Ho et al. found IEM as a primary motility abnormality in patients with GERD, with overall incidence of 49.4% [11]. Non-obstructive dysphagia is frequently associated with severe peristaltic dysfunction in patients with GERD [19]. Dominigues et al. demonstrated that GERD patients show several pathological features including delayed bolus transport, impaired propulsive volume clearance, pathological transport patterns and pathological reflux patterns [20].

Multiple studies showed esophageal peristaltic dysfunction was increasingly prevalent with more severe GERD presentation, from non-erosive reflux disease (NERD) to erosive esophagitis (ERD) and Barrett’s esophagus [21–23].

In patients with GERD-associated respiratory symptoms, IEM was the most common esophageal dysmotility, where 53% of patients with asthma, 41% with chronic cough, and 31% with laryngitis-associated GERD had IEM [24].

**IEM and GERD**

maximizing acid suppression is of paramount importance, and addition of a histamine-2 receptor antagonist at night improves GERD symptoms for patients already on proton pump inhibitors (PPI) [25]. Using impedance-pH monitoring, it has been shown that more than one third of GERD patients have persistent symptoms

**Table 1** Conditions associated with ineffective esophageal motility (IEM)

<table>
<thead>
<tr>
<th>Condition</th>
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<tbody>
<tr>
<td>Gastroesophageal reflux disease (GERD)</td>
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<tr>
<td>Barrett’s esophagus</td>
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<tr>
<td>Diabetes mellitus with autonomic dysfunction</td>
</tr>
<tr>
<td>Amyloidosis</td>
</tr>
<tr>
<td>Acute ethanol ingestion</td>
</tr>
<tr>
<td>Chronic alcoholism with neuropathy</td>
</tr>
<tr>
<td>Esophageal adenocarcinoma</td>
</tr>
<tr>
<td>Endoscopic submucosal dissection (ESD)</td>
</tr>
<tr>
<td>Eosinophilic esophagitis</td>
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<td>Rheumatic disease</td>
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**Fig. 1** Ineffective swallows in a patient with severe ineffective esophageal motility (IEM), accompanied by defective bolus transit (DBT) on impedance measurement to liquid swallows (LS). UES upper esophageal sphincter, LES lower esophageal sphincter

**Treatment**

Maximizing acid suppression is of paramount importance, and addition of a histamine-2 receptor antagonist at night improves GERD symptoms for patients already on proton pump inhibitors (PPI) [25]. Using impedance-pH monitoring, it has been shown that more than one third of GERD patients have persistent symptoms.
despite PPI treatment, attributed mainly to non-acid reflux [26].

Transient LES relaxation (TLESR), which is defined as LES relaxation not proceeded by a swallow, is widely considered a major mechanism of GERD [27]. Baclofen, a reflux inhibitor, is a γ-aminobutyric acid (GABA) β-receptor agonist, which interferes with the TLESR mechanism. Despite the initial promising results, baclofen use has been limited by the adverse events profile and small therapeutic gain [28, 29].

Pro-kinetic drugs were found to result in a significant rise in peristaltic distal esophageal amplitude (DEA). A double-blind randomized study in healthy volunteers showed enhancement in esophageal motility with the use of pro-kinetic agents: buspirone, a serotonin 5-hydroxytryptamine 1A and 5-hydroxytryptamine 2 receptor agonist; pyridostigmine, a cholinesterase inhibitor; and bethanechol, a direct-acting muscarinic receptor agonist. All three agents significantly increased mean DEA and mean LES resting pressure for saline swallows during the 1 h post dosing [30]. Another study showed that in addition to increasing DEA, bethanechol treatment resulted in a significant improvement in bolus transit in patients with severe IEM [31].

Another pro-kinetic agent, cisapride significantly improved ineffective esophageal peristalsis, as well as bolus clearance, but its use has been stopped in the USA due to occurrences of ventricular arrhythmias [32, 33]. Mosaprid, which enhances gastrointestinal motility by acting on 5-hydroxytryptamine 4 receptors, improved esophageal sensitivity of secondary peristalsis but had limited effect on the motor properties of secondary peristalsis in IEM patients [34].

Currently, surgery represents the only reliable way to restore the integrity of the LES. Fundoplication was shown to reduce the rate of TLESR. Particularly, reflux-associated TLESR rate was found to be decreased after fundoplication [35, 36]. Preoperative assessment of patients being considered for anti-reflux surgery is recommended to exclude severe motility abnormalities [16]. In IEM patients, preoperative manometry may help determine the best surgical approach, where a partial fundoplication like Toupet (270°) or Dor (180°) might be a more preferable option to Nissen (360°) fundoplication, aiming to decrease post-fundoplication dysphagia. In addition, performing multiple rapid swallows (MRS) test to assess the “peristaltic reserve” has been advocated prior to anti-reflux surgery in IEM patients [9].

Laparoscopic magnetic sphincter augmentation (MSA) with LINX™ device is a novel therapy for GERD [37]. It augments the lower esophageal sphincter barrier without altering gastric anatomy and is easily reversible [38]. The device reduced abnormal esophageal acid exposure time, improved reflux symptoms and quality of life, and allowed cessation of PPI therapy in majority of patients in two single-center trials [38]. Recent comparative studies demonstrated MSA with LINX™ as a safe and effective alternative to fundoplication for treatment of GERD [37, 39].

Transoral incisionless fundoplication (TIF) is another novel anti-reflux procedure. Prospective multicenter U.S. study-year results showed that TIF safely achieved sustained symptomatic control, normalization of esophageal acid exposure, and healing of existing esophagitis in two thirds of patients without major side effects related to the procedure itself [40]. Recent randomized, placebo controlled trial demonstrated TIF as an effective treatment for patients with GERD symptoms, particularly in those with persistent regurgitation despite PPI therapy, based on evaluation 6 months after the procedure [41]. Our opinion is a longer-term follow-up is required to ensure patients’ safety and persistence of the positive effect to these relatively new procedures.
Evolution of IEM as a Motility Abnormality

Ineffective motility of the esophagus has evolved from initial description as “atypical manometry” into nonspecific esophageal motility disorder (NEMD) where 30% or more of the wet swallows showed any combination of non-transmitted or low-amplitude contractions [3], either of which result in impaired volume clearance on concomitant videofluoroscopy and manometry. A contraction amplitude of <30 mmHg was shown to be associated with abnormal bolus movement [4]. A more precise terminology for NEMD was proposed in 1997 as ineffective esophageal motility (IEM), since the vast majority of NEMD patients had ≥30% swallows of amplitude<30 mmHg [2]. A higher threshold for IEM, requiring ≥50% of wet swallows to be ineffective, was subsequently proposed on combined impedance-manometry to have more clinical and functional relevance [6, 7]. The unifying feature of swallows contributing to a diagnosis of IEM is the poor bolus transit in the distal esophagus [9], and more severe IEM appears to be associated with abnormal bolus transit. We find the term of defective bolus transit (DBT) is useful as a more descriptive term for the functional defect associated with this manometric finding. The dilemma in diagnosing the difficult-to-interpret manometric studies continues to be a challenge in the field, and we find that the category of major motility abnormality (MMA) to be helpful in this regard. This diagnosis is only made infrequently (around 5% of cases) and is reserved for impedance-manometry studies where two abnormal motility disorders are being considered. Figure 3 illustrates the evolution of the definition of IEM over the years.

Conclusion

Ineffective esophageal motility (IEM) is a common abnormal motility finding encountered in patients referred to esophageal motility laboratories. Association with GERD is well-documented, and IEM is more prevalent in patients with more advanced reflux disease. Patients with IEM present with various complaints, but a more severe peristaltic dysfunction may present with dysphagia and a defective bolus transit (DBT). Advancement in diagnostic technology (high resolution manometry, intraluminal impedance, and 24-h pH-impedance reflux monitoring) has shed more light on the condition. IEM appears to subdivide into two groups; a more severe form that manifests with dysphagia and is associated with a more defective bolus transit and a milder form of which the clinical significance is not very clear. Further study of functional aspect of swallows in IEM patients, by measuring the integrity of bolus transit to liquid, viscous, and possibly solid and multiple rapid swallows, may represent a more meaningful way to assess the severity of the disease, where disease progression could be assessed not only by esophageal pressure (amplitude or DCI) but also by the severity of the dysfunction measured by how defective is the bolus transit. Despite advances in diagnostic tests (HRM, impedance measurement), IEM remains an under-recognized and under-treated condition. Effective treatment persists as a challenge, where more studies (especially of prospective nature) are required to elucidate on effective treatment to restore peristalsis and to improve symptoms and function in patients with severe IEM.
Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

Human and Animal Rights and Informed Consent Among cited articles where one of the authors of the current report was an author, local institutional review board approval was obtained and maintained for studies where human (or animal) subjects research was performed.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
• Of major importance


42. Tutuian R, Castell DO. Combined multichannel intraluminal impedance and manometry clarifies esophageal function abnormalities: study in 350 patients. Am J Gastroenterol. 2004;99(6):1011–9. **This paper describes the functional defect in IEM patients on impedance measurnet.**

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