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How to Optimally Apply Impedance in the Evaluation of Esophageal Dysmotility

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Abstract

The utilization of impedance technology has enhanced our understanding and assessment of esophageal dysmotility. Esophageal high-resolution manometry (HRM) catheters incorporated with multiple impedance electrodes help assess esophageal bolus transit, and the combination is termed high-resolution impedance manometry (HRIM). Novel metrics have been developed with HRIM—including esophageal impedance integral ratio, bolus flow time, nadir impedance pressure, and impedance bolus height—that augments the assessment of esophageal bolus transit. Automated impedance-manometry (AIM) analysis has enhanced understanding of the relationship between bolus transit and pressure phenomena. Impedance-based metrics have improved understanding of the dynamics of esophageal bolus transit into four distinct phases, may correlate with symptomatic burden, and can assess the adequacy of therapy for achalasia. An extension of the use of impedance involves impedance planimetry and the functional lumen imaging probe (FLIP), which assesses esophageal biophysical properties and distensibility, and could detect patterns of esophageal contractility not seen on HRM. Impedance technology, therefore, has a significant impact on esophageal function testing in the present day.

Keywords

High-resolution manometry (HRM); High-resolution impedance manometry (HRIM); Impedance; Esophageal dysmotility; Esophageal bolus transit; Functional lumen imaging probe (FLIP)

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and were in compliance with all applicable ethical standards (including the Helsinki Declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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Introduction

The widespread availability of esophageal high-resolution manometry (HRM) has improved the recognition and categorization of esophageal motor patterns and has enhanced the clinical utility of esophageal motor testing. Three important software tools evaluate esophageal motor function [1•]. The most intuitive of these is the integrated relaxation pressure (IRP), which measures nadir pressure during expected swallow-induced relaxation of the lower esophageal sphincter (LES). Software tools also interrogate the vigor of esophageal smooth muscle contraction (distal contractile integral (DCI)) and timing of peristalsis (distal latency (DL)). DCI estimates the “area under the curve” of esophageal smooth muscle contraction, taking length, duration, and amplitude of contraction into consideration. Timing of peristalsis is measured using DL, which records the time from initiation of a swallow to the inflection point between fast velocity in the esophageal body and slower velocity at the emptying phase in the distal esophagus, termed the contractile deceleration point (CDP). An international consensus of HRM experts developed and endorsed the Chicago Classification of motor disorders, now in version 3.0, which has promoted the utilization of uniform parameters to characterize esophageal peristalsis in health and disease [1•].

Impedance technology was initially popularized as part of pH-impedance monitoring to enhance the detection of reflux events and increase the yield of symptom-reflux correlation [2, 3]. However, in conjunction with HRM, stationary impedance is utilized, rather than ambulatory impedance monitoring [4]. When pairs of electrodes are incorporated into the HRM catheter, impedance (i.e., resistance to flow of tiny currents) can be measured and displayed in the HRM color topography plot (Clouse plot). When bolus is present within the esophagus adjacent to the electrodes, intraluminal impedance drops but returns to baseline when the bolus moves past each pair of electrodes. The drop in impedance typically precedes the contraction sequence. Impedance data from several pairs of electrodes can be assimilated using dedicated software and displayed superimposed on pressure topography plots, thereby allowing visualization of the bolus as it travels down the esophagus. High-resolution impedance manometry (HRIM) catheters are therefore incorporated with multiple impedance sensors in addition to high-fidelity circumferential pressure sensors. This advancement allows for the study of bolus transit in conjunction with assessment of esophageal motor phenomena, using HRIM.

HRIM provides an additional dimension in the assessment of esophageal physiology and pathophysiology by providing information on what the bolus does in conjunction with peristalsis [4, 5]. Impedance-detected bolus presence has been demonstrated to correlate well with videofluoroscopic assessment, suggesting that HRIM data can be utilized as a surrogate for barium radiographs in some settings [6•]. For esophageal studies involving HRIM, boluses of saline (which have better conductivity) are utilized rather than water boluses to maximize visualization on impedance contour plots [7]. An extension of impedance technology, impedance planimetry (IP), has recently gained notoriety as a means of evaluating esophageal luminal cross-sectional area using distension of a balloon catheter containing impedance electrodes, allowing for assessment of distensibility, compliance, and biophysical properties (Table 1).

Evaluation of Bolus Transit

Although esophageal bolus transit is primarily dependent on the intraluminal pressures measured by HRM, the correlation between esophageal peristalsis and effectiveness of bolus transit is complex and imperfect [8]. For example, HRIM has confirmed complete bolus transit in patients with contraction amplitudes as low as 20 mmHg in the absence of large peristaltic breaks [9]. Despite the imperfect relationship between bolus transit and pressure phenomena, combined HRIM and videofluoroscopy testing has demonstrated that impedance monitoring can evaluate bolus stasis and clearance with strong concordance to barium studies in both healthy controls and those with non-obstructive dysphagia [6•]. An advantage of HRIM is that it is free from the radiation exposure associated with barium studies.

Using the actual impedance tracings acquired concurrently with HRM, new impedance metrics have been identified that have relevance to the evaluation of bolus transit. For instance, the point of nadir impedance preceding a contraction wave can be identified. This metric is significant, because the pressure at the point of nadir impedance represents the intrabolus pressure (IBP) [10]. The time from the point of nadir impedance to the point of peak pressure in the ensuing peristaltic sequence is also clinically relevant and correlates with the perception of dysphagia [11•]. If the point of nadir impedance is too close to the point of peak contraction, bolus transit may be abnormal because of bolus trapping, and dysphagia can result.

Impedance-based metrics such as nadir impedance have been subject to automated impedance-manometry (AIM) analyses using MATLAB-based algorithms. AIM analyses predict abnormal bolus transit from the comparison of impedance-derived metrics to pressure data [11•]. Across varying consistencies of swallowed boluses (liquid, semi-solid, solid), nadir impedance and impedance at peak pressure were the two metrics out of eight esophageal function variables derived by AIM that consistently and significantly distinguished patients with dysphagia from normal controls, with both metrics lower in dysphagia. A threshold of 2400 Ω for impedance at peak pressure predicted dysphagia symptoms with sensitivity 0.83, specificity 0.93, and kappa agreement 0.77 [11•]. Further, in a comparison of non-obstructive dysphagia patients with normal esophageal manometry studies to healthy controls [12], patients with non-obstructive dysphagia had higher IBP and nadir impedance pressures as well as shorter time intervals between nadir impedance and peak pressures when compared to healthy controls, implying that AIM increases the sensitivity of detection of subtle abnormalities in patients with non-obstructive dysphagia [12] (Fig. 1). In this manner, AIM pressure-flow parameters can distinguish normal patients from those with dysphagia as well as correlate motor phenomena with patient perception of esophageal bolus stasis, providing insight into bolus transit when esophageal peristalsis is intact [11•].

On the other hand, when there are breaks in the esophageal peristaltic integrity, or if peristalsis fails, the bolus may remain in the esophageal lumen. The likelihood of bolus escape is very high with breaks ≥ 5 cm in the peristaltic contour, using an isobaric contour threshold of 20 mmHg, but the association with dysphagia remains imperfect [9].

Quantitation of bolus escape has been problematic; no reliable clinical metric is yet available, but research continues toward development of an optimal software tool. The most intuitive among the metrics being studied is the esophageal impedance integral (EII) [13]. Using sophisticated software algorithms, HRIM topography plots can be interrogated to generate a measure of bolus retention both prior to and following a peristaltic sequence. The ratio between bolus presence *after* a peristaltic sequence and bolus presence *before* the sequence is termed the EII ratio. The EII ratio is significantly different between normal peristalsis (where no bolus is present after a peristaltic sequence), peristalsis with breaks (where some bolus is present after a peristaltic sequence), and absent peristalsis (where bolus presence may be similar before and after the anticipated peristaltic sequence). The EII ratio on supine HRIM showed a strong correlation with videofluoroscopic findings ($r=0.96$) [13].

HRIM with videofluoroscopy has been utilized to model the dynamics of bolus transit into four distinct phases: (a) upper esophageal sphincter (UES) opening, (b) UES closure to transition zone, (c) transition zone to contractile deceleration point (CDP), and (d) CDP to bolus emptying completion [10]. Specifically, description of these phases relies upon the classification of IBP into functional components based on mechanical states of the esophageal wall, suggesting that abnormalities in IBP may assist in the elucidation of esophageal pathology subtypes [10].

Provocative testing during esophageal HRM is gaining acceptance as part of a standard esophageal manometry protocol. Augmentation of esophageal body peristalsis during provocative maneuvers such as multiple rapid swallows (MRS) evaluates peristaltic reserve [14]. Esophageal outflow obstruction can be precipitated by the higher bolus volume associated with multiple water swallows (MWS, also known as free water drinking) or solid test meals [15]. These provocative tests can be enhanced by the ability to visualize the bolus with HRIM [16].

Assessment of Belching and Regurgitation

Impedance technology has been successfully utilized in the evaluation of belching and regurgitation symptoms. Because impedance sensors can detect gas movement, impedance monitoring can differentiate supragastric belching (where air rapidly enters and subsequently exits the esophagus without reaching the stomach) from gastric belching (where air from the stomach is expelled orally) in patients with aerophagia, thus guiding management [17]. Further, the combination of manometry with impedance, available as impedance-conventional manometry as well as HRIM, can distinguish rumination syndrome, where undigested food is regurgitated from the stomach, from both supragastric and gastric belching [18]. For the assessment of such symptoms, a prolonged study is performed (typically 1 h) that involves the administration of a standardized meal with the HRIM catheter in place, followed by a period of post-prandial monitoring to assess for bolus movement and manometric patterns. An early rise in intragastric pressure preceding the peak pressure seen with intraabdominal straining is suggestive of rumination syndrome [19]. Consequently, the combination of HRIM can also help distinguish rumination episodes from

regurgitation events associated with gastroesophageal reflux disease during transient LES relaxation, by the presence of gastric pressure peaks >30 mmHg in rumination [20] (Fig. 2).

Classification of Esophageal Motor Disorders

The assessment of esophageal bolus transit from the use of HRIM has contributed significantly to current metrics utilized in the Chicago Classification of esophageal motor disorders. For instance, the concept of peristaltic integrity at 20 mmHg being adequate for bolus transit was determined with the use of HRIM; peristaltic sequences with breaks <2 cm in the 20 mmHg isobaric contour were associated with complete bolus clearance by impedance criteria using HRIM [21]. Although the previous version of the Chicago Classification (version 2.0) included small breaks (2–5 cm) as part of the motor disorder spectrum, these small breaks were demonstrated not to be pathognomonic of abnormal bolus transit in subsequent studies [9] and were also identified in normal controls [22].

Similarly, the concept of large (>5 cm) breaks in the 20 mmHg isobaric contour being relevant for incomplete bolus transit comes from data acquired with HRIM [9]. HRIM data has contributed to the criteria developed for the diagnosis of fragmented peristalsis and ineffective esophageal motility (IEM) in the newest Chicago Classification (version 3.0) [1•]. It is likely that concurrent impedance measurements will be incorporated into future versions of the Chicago Classification, to measure the impact of esophageal pressure abnormalities on bolus transit as well as to enhance esophageal function analysis in patients without major motor abnormalities [1•].

Clinical Assessment of Achalasia

Before endoscopic or surgical therapy to disrupt the lower esophageal sphincter (LES) in achalasia, HRIM can be utilized to assess bolus retention in the esophagus; after therapy, this can assess the adequacy of LES disruption. When a 200-mL water challenge is administered with the patient standing up during an HRIM study, the water column within the esophagus can be quantified as the impedance bolus height (IBH) at the end of 5 min, using HRIM topography plots showing bolus retention (or lack thereof) in the esophageal body [23•]. The IBH correlated well with the height of the barium column on timed upright barium studies at similar time intervals in a series of achalasia patients, half of whom were treatment naive and the other half assessed after variable methods of LES disruption as therapy for their achalasia [23•]. Moreover, in another cohort of treated achalasia patients, this correlation between the IBH and barium column height remained strong at a median follow-up of over 3 years after therapy, regardless of Eckardt score [24]. Therefore, IBH can be used as a surrogate for the timed upright barium swallow in addressing adequacy of LES disruption in achalasia.

HRIM has also been utilized to assess flow across the esophagogastric junction (EGJ) [25]. Bolus flow time (BFT) represents decline in resting pressures across the EGJ concurrent with decline in impedance values at the same levels at the EGJ, signifying periods during which a liquid bolus can flow through the EGJ [25, 26•]. Further, the median BFT was significantly lower in treatment-naive achalasia patients compared to controls and in

achalasia subtype 1 compared to subtype 2, in both supine and upright positions. After LES disruption, BFT was more representative of residual symptom burden in contrast to the integrated relaxation pressure (IRP) typically utilized for achalasia diagnosis in treatment-naïve patients [26•]. BFT has potential to become an important metric in assessing EGJ function following LES disruption in achalasia.

Impedance Planimetry and Functional Lumen Imaging Probe

Impedance planimetry, the precursor of the present-day functional lumen imaging probe (FLIP), was used in the mid-1990s to assess changes in esophageal cross-sectional area with esophageal contraction in response to balloon distension [27]. Multiple impedance sensors are housed in a highly compliant balloon, which can be filled with conducting fluid of varying volumes. Since the current passed between the electrodes, the volume of distension, and the conductivity of the fluid used for distension are known, the measured impedance is a function of the area of distribution of the volume, thus allowing for the assessment of the cross-sectional area adjacent to an impedance electrode [28]. This technique facilitated assessment of change in esophageal cross-sectional area in response to balloon distension, and early reports demonstrated a hyperreactive and poorly compliant esophagus in non-cardiac chest pain [27].

The modern version of impedance planimetry, termed EndoFLIP (Crospon Inc., Galway, Ireland), uses the same biophysical concepts. The FLIP device consists of a probe onto which a highly compliant polyurethane balloon (that assumes a cylindrical shape with volumetric distension) is mounted, equipped with a solid-state pressure transducer to measure intraballoon pressure, as well as closely spaced impedance electrodes to acquire cross-sectional area measurements along the length of the balloon [29]. The relationship between cross-sectional area and intrabag pressures can be depicted as the distensibility index (DI) [30]. The DI was initially used to study the EGJ, particularly in achalasia before and after LES disruption, where poor esophageal symptomatic outcomes were demonstrated to correlate with a low DI [30]. Similarly, other investigators have reported the value of FLIP measurements during myotomy and following LES disruption in achalasia [31–33] (Fig. 3).

In addition to assessment of the adequacy of LES disruption, FLIP may also serve as a “smart bougie” during fundoplication to evaluate the orientation and position of the wrap. This may enhance surgical training and potentially improve surgical outcomes by guiding intraoperative modification of the wrap by providing real-time data on tightness of the wrap [34, 35]. As would be expected, EGJ distensibility measured intraoperatively with FLIP is less restricted after partial 270° Toupet compared to full 360° Nissen fundoplication [36]. Given these findings, because of its ability to assess EGJ distensibility, it follows that FLIP could have potential value in minimizing overly restrictive wraps and thus reducing the potential for post-fundoplication dysphagia and gas-bloat syndrome [37]. Normal distensibility of the healthy esophagus has been evaluated, demonstrating that the distal esophagus is more distensible than the proximal esophagus [38]. In comparison, the esophagus in eosinophilic esophagitis is poorly distensible, and FLIP measurements have been used in the prediction of food impaction risk as well as the need for therapeutic dilation in eosinophilic esophagitis [39].

Taking these concepts further, cross-sectional area, measured using FLIP, can provide insights into both failure of LES relaxation and esophageal body contraction patterns in achalasia subtypes [40•]. Topographic depiction of changes in cross-sectional area in relationship to time and esophageal length has been termed FLIP topography. Preliminary evaluations suggest that secondary peristaltic sequences in response to esophageal distension with the FLIP balloon generate characteristic changes in cross-sectional area in health and in esophageal outflow obstruction. For instance, changes in cross-sectional area suggestive of repetitive antegrade contractions are seen in healthy individuals, with normal distensibility of the EGJ. Cross-sectional area in the esophageal body tends to appear constant without changes, with poor distensibility of the EGJ, in type 1 achalasia. Both antegrade and retrograde contractions are seen in type 2 achalasia, in conjunction with poor EGJ distensibility. Type 3 achalasia was associated with repetitive retrograde contractions, which could represent markers of esophageal outflow obstruction [40•]. Therefore, patterns of esophageal contractility not seen on HRM or HRIM may be detected with FLIP topography, potentially allowing categorization of esophageal outflow obstruction into achalasia subtypes using FLIP topography alone. These advanced uses of impedance are now at the cutting edge of esophageal function testing but are not yet ready for clinical use, as research continues toward optimal utilization of these techniques.

Conclusions

The application of impedance technology to esophageal HRM as well as the development of impedance planimetry—most notably with FLIP—has augmented our understanding of esophageal motor function and dysmotility. HRIM assesses esophageal bolus stasis and transit with good correlation to videofluoroscopy, but without radiation exposure. The development and better understanding of impedance-based metrics, such as IBP, nadir impedance pressures, EII ratios, and BFT, enhance our ability to better understand and assess bolus transit dynamics, especially with the development of automated impedance-manometry. HRIM has contributed to the Chicago Classification of esophageal motor disorders and will likely play an even more significant role in future iterations of the classification. In achalasia, IBH correlates with videofluoroscopy to assess bolus transit across the esophagogastric junction and can be utilized both before and after therapy with disruption of the LES. Finally, FLIP not only has the potential to evaluate the adequacy of achalasia treatment and risk of food impaction in eosinophilic esophagitis but may also detect esophageal contractility in achalasia patients that is not visualized on HRM studies, with potential implications for symptomatic outcomes and management. In sum, the application of impedance in the evaluation of esophageal dysmotility is rapidly advancing and is likely to contribute to our understanding of esophageal motor dysfunction in the years to come.

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Fig. 1.

Automated impedance manometry. Esophageal impedance and pressure signals with automated impedance manometry (AIM) metrics. **a** Relationship between impedance tracing (purple) and pressure wave (black). The drop in impedance coincides with bolus transit antecedent to rise in pressure amplitude. The pressure at point of nadir impedance (PNadImp) represents intrabolus pressure. The time at nadir impedance (TNadImp) to peak pressure (PeakP) can be useful in assessing bolus transit. **b** In a normal control subject, *iso-contours* depict pressure changes and *horizontal lines* depict impedance changes during 5-mL viscous bolus swallow. TNadImp consistently precedes PeakP as the peristaltic sequence moves down the esophagus. **c** In a patient with non-obstructive dysphagia but normal manometry, the TNadImp is shifted rightward and tracks much closer to PeakP compared to normal controls, suggesting abnormal bolus transit. Reproduced with permission from John Wiley and Sons from [12]

Fig. 2.

Use of high-resolution manometry and pH-impedance to identify rumination. Increase in gastric pressure is seen preceding the retrograde flow of gastric contents through the esophagus, concurrent with increase in esophageal pressures in retrograde fashion followed by subsequent UES relaxation. Reproduced with permission from Nature Publishing Group from [20]

Fig. 3. Functional lumen imaging probe (FLIP) utilized for assessment of distensibility of the esophagogastric junction (EGJ) prior to and following per-oral endoscopic myotomy (POEM). The EGJ has a small cross-sectional area (depicted in *blue* in **a**) prior to disruption, indicating poor distensibility. Following POEM (**b**), the cross-sectional area increases, indicating successful myotomy. Reproduced with permission from Springer from [33]

Table 1

Clinical and research uses of impedance technology in esophagology

Clinical	Research
pH-impedance monitoring for assessment of reflux burden	Esophageal impedance integral (EII) ratios from HRIM studies for quantitative assessment of esophageal bolus retention
HRIM monitoring to assess antegrade and retrograde air and fluid movement in the diagnosis of supragastric and gastric belching and rumination syndrome	HRIM assessment of bolus transit in relationship to peristaltic integrity, utilized for development of criteria for effective vs. ineffective sequences and relevance of peristaltic breaks
HRIM assessment of esophageal bolus transit and stasis, with standard ten-swallow sequence as well as with provocative testing	Automated impedance manometry (AIM) analysis for evaluation of bolus transit in non-obstructive dysphagia
HRIM impedance bolus height (IBH) as surrogate for timed upright barium swallow in achalasia, especially following LES disruption	HRIM with videofluoroscopy to model phases of esophageal bolus transit and classification of IBP Bolus flow time (BFT) to assess adequacy of EGJ disruption in achalasia
FLIP to assess adequacy of EGJ disruption in achalasia	FLIP to detect patterns of esophageal contractility in response to esophageal distension in esophageal outflow obstruction FLIP to predict food impaction risk in eosinophilic esophagitis