Clinical Applications of Esophageal Multichannel Intraluminal Impedance Testing

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Abstract: Multichannel intraluminal impedance is a relatively new technology that allows detection of bolus movement in the gastrointestinal tract without the use of radiation. In clinical applications it is combined with manometry, allowing a better evaluation of the functional characteristics (ie, bolus transit) of esophageal motility abnormalities. When combined with pH monitoring, it provides more comprehensive data on both acid and nonacid gastroesophageal reflux.

First described in 1991 by Silny,1 esophageal multichannel intraluminal impedance (MII) detects bolus movement by measuring the resistance of intraluminal content to alternating current (AC). The basic components of the impedance circuit include an AC generator connected to 2 metal rings. The rings are separated by an isolator (ie, the body of the catheter) so, for the circuit to be closed, electrical charges have to be carried by ions surrounding the catheter. Changes in impedance are determined by the ionic concentration around the catheter. In an empty esophagus there are only a few ions present, mainly in the esophageal mucosa. When a liquid bolus is present between the rings, the ionic load increases, allowing better electrical conductivity and registration by the circuit of low impedance (Figure 1).

The movement of a bolus past the two rings is identified by the following changes, which have been validated by combined video-fluoroscopy-impedance studies. The relatively stable baseline impedance of the empty esophagus declines rapidly, once the liquid bolus enters the impedance-measuring segment. This drop is occasionally preceded by a short-lived rise in impedance, produced by a small pocket of air traveling ahead of the bolus. As long as the bolus is present between the rings, the impedance will be low and will start rising when the bolus stops making contact with the first metal ring, returning to baseline when the bolus exits the segment (ie, loss of contact with the second ring). Occasionally, a small increase in impedance can be observed as esophageal muscle contraction decreases the cross-section of the esophageal lumen. By convention,
Studies using combined videofluoroscopy and impedance and studies using combined scintigraphy and impedance have been performed in order to validate the ability of MII to detect bolus movement.2,3 Considering bolus entry at a 50% drop in impedance from baseline to nadir and bolus exit at the recovery of impedance to the 50% value, Simren and colleagues4 found a strong correlation between both methods for measurement of the time to esophageal filling ($r^2=0.89$; $P<.0001$) and time to esophageal emptying ($r^2=0.79$; $P<.0001$). More recently Iman and coworkers5 reported on the correlation between MII and barium swallows in 13 healthy volunteers indicating that barium and impedance bolus transit or stasis was correlated in 97% (72/74) of swallows.

Combined Esophageal Impedance-Manometry Testing

The need for a method that allows a more comprehensive evaluation of esophageal function rose from the suboptimal correlation between esophageal peristalsis assessed by manometry and bolus transit assessed by imaging studies. Videofluoroscopy is the gold standard for assessing esophageal bolus transit while esophageal manometry is considered the gold standard for assessing and quantifying esophageal peristalsis. Unfortunately, in clinical practice, these tests are performed during separate sessions, thereby evaluating different sets of swallows. Combined videofluoroscopy-manometry systems used in clinical research have limited acceptance in routine clinical practice because the radiation exposure limits the number of swallows available for analysis and the combined evaluation requires a more complex coordination of equipment and personnel.

Combined impedance manometry has the ability to overcome these limitations. The addition of impedance capability to conventional manometry catheters does not change the dimensions of the catheter utilized in this test. From a patient perspective, it is no different from conventional manometry. Because it does not require radiation, it allows analysis of an unlimited number of swallows. By recording bolus transit and pressure data during the same swallows, it allows a better evaluation of the functional aspects (ie, bolus transit) of individual contractions.

One currently available combined MII-EM [AU: ELECTROMANOMETRY?] system uses a 9-channel MII-EM catheter (Konigsberg Instruments Inc., Pasadena, CA). This catheter has 5 solid state pressure transducers located at 5 cm, 10 cm, 15 cm, 20 cm, and 25 cm from the tip of the catheter and 4 pairs of metal rings, 2 cm apart (impedance measuring segments) centered at 10 cm, 15 cm, 20 cm, and 25 cm from the tip of the catheter; thus straddling the 4 proximal pressure transducers. During esophageal testing, the distal pressure transducer...
is placed in the lower esophageal sphincter (LES) high-pressure zone with the combined impedance and pressure transducers at 5 cm, 10 cm, 15 cm, and 20 cm above the LES (Figure 4). Both pressure and bolus transit data are analyzed using a computer-based semi-automated program (Bioview, Sandhill Scientific).

The combination of impedance and manometry provides the opportunity to describe and quantify the functional aspects of esophageal contractions. Traditional manometry classifies swallows into (1) normal peristaltic (defined as contraction amplitude in the distal part of the esophagus of at least 30 mm Hg and onset velocity in the distal esophagus not greater than 8 cm/sec), (2) simultaneous contractions (defined as contraction amplitude in the distal part of the esophagus of at least 30 mm Hg and distal onset velocity greater than 8 cm/sec) and (3) ineffective contractions (defined as contraction amplitude in the distal part of the esophagus less than 30 mm Hg). MII complements this information and defines swallows as having either (1) complete bolus transit (defined as detection of bolus exit in all 3 of the distal impedance channels) or (2) incomplete bolus transit (defined as absence of bolus exit in any of the 3 distal impedance channels). Combining the information from MII and manometry allows assessment of bolus transit during manometrically normal peristaltic, simultaneous, or ineffective esophageal contractions (Figure 5).

A multicenter study in 43 healthy volunteers established normal values for esophageal function testing using combined MII-EM. In healthy volunteers almost all manometrically normal swallows achieved complete bolus transit (99.5% and 97.7% for liquid and viscous boluses, respectively). For the occasional simultaneous contractions occurring in these healthy subjects all (100%) of liquid and more than half (54.5%) of viscous swallows achieved complete bolus transit. For the occasional ineffective contractions of almost two thirds (61.9%) liquid and more than one third (39.1%) of viscous swallows had complete bolus transit (examples are shown in Figure 5).

This study offered the opportunity to propose criteria for normal or abnormal bolus transit during standard MII-EM testing. Normal transit for a series of 10 liquid swallows (5 ml each) was defined by 8 or more (80%) swallows with complete bolus transit. The corresponding value for 10 viscous swallows (5 ml each) was 7 out of 10 (70%) swallows with complete transit. These results underscore the functional effectiveness of a normal peristaltic progression and indicate that combined MII-EM will identify which manometrically abnormal studies are functionally defective.

Nguyen and associates have recently reported normal data for a combined water-perfused manometry–impedance system in a group of 42 healthy volunteers.
Although there were some differences between individual parameters obtained from this system when compared to those published from the solid-state manometry–impedance system, the overall number of swallows with complete bolus transit during both saline and viscous swallows were similar.

Studying 350 consecutive patients with various manometric findings undergoing combined MII-EM, we subsequently evaluated the ability of MII to characterize bolus transit abnormalities in different groups of patients. All patients with achalasic and sclerodermic esophagus were found to have abnormal rates of bolus transit for liquid (ie, incomplete bolus transit for at least 30% of liquid swallows) and viscous (ie, incomplete bolus transit for at least 40% of liquid swallows). Normal bolus transit for liquid was identified in at least 95% of patients with normal manometry, nutcracker esophagus, and isolated LES abnormalities (ie, poorly relaxing LES, hypertensive and hypotensive LES). Approximately half of patients with ineffective esophageal motility (IEM) and distal esophageal spasm (DES) had normal bolus transit for liquid (Figure 6).

A more detailed study in 70 patients with ineffective esophageal motility illustrate the fact that there is no perfect (ie, highly sensitive and highly specific) manometric cutoff to predict complete bolus transit and that the current manometric criteria for diagnosing IEM (ie, 30% or more manometrically-identified ineffective swallows) is too sensitive and lacks the specificity for identifying patients with abnormal bolus transit. Normal bolus transit in the group of patients with IEM appeared to be dependent on the distal esophageal amplitude (ie, average amplitude at 2 distal esophageal sites, 5 cm and 10 cm above the LES), the number of sites with low contraction amplitudes, and the overall number of manometrically ineffective swallows. Separating patients with 3 and 4 manometrically ineffective swallows from those with 5 or more ineffective swallows we found that the majority of patients in the first group had normal bolus transit, whereas the majority of patients in the second group had abnormal bolus transit. These data indicate that 5 or more manometrically ineffective swallows provides a better separation of IEM patients with abnormal bolus transit and suggests that currently used manometric criteria to identify IEM should be revised. Another important finding of this study was that approximately one third of patients with IEM had normal bolus transit for liquid and viscous swallows (suggesting a mild functional defect), approximately one third had abnormal bolus transit for either liquid or viscous swallows (moderate functional defect) and the remaining third of IEM patients had abnormal bolus transit for both liquid and viscous swallows (severe

Figure 5. Examples of combined multichannel intraluminal impedance–electromanography (MII-EM) tracings in patients. MII channels are in the upper part and EM channels in the lower part of the tracings. Swallows shown are manometric normal with complete bolus transit (a), manometric ineffective with complete (b) or incomplete (c) bolus transit and simultaneous with complete (d) or incomplete (e) bolus transit. [AU: PLEASE PROVIDE ORIGINAL DIGITAL IMAGE]

Figure 6. Percentage patients with normal bolus transit for liquid based on manometric diagnoses. IEM = ineffective esophageal motility; DES = distal esophageal spasm; LES = lower esophageal sphincter.
functional defect). Outcomes studies are warranted to evaluate whether grading of esophageal function defect in patients with manometric IEM has the potential to identify patients at risk for developing post-operative dysphagia following antireflux surgery (ie, those with severe functional defect).

Analyzing a group of 71 patients with distal esophageal spasm (DES), we found that manometrically simultaneous swallows were more likely to have complete bolus transit if they had high amplitude and an antegrade contraction onset in the distal esophagus. Clinically, DES patients were found to be a heterogeneous group presenting with various esophageal symptoms. Evaluating the overall bolus transit during 10 liquid and 10 viscous swallows, we found that approximately half of patients with manometric criteria of DES have normal bolus transit. About a quarter of DES patients had abnormal bolus transit for both liquid and viscous swallows (severe functional defect) and the remaining quarter had abnormal bolus transit for either liquid or viscous (moderate functional defect). Patients presenting with chest pain had higher contraction amplitudes and were more likely to have normal bolus transit compared to patients presenting with dysphagia or GERD symptoms. At this point, similar to the situation in the group of patients with IEM, outcomes studies are warranted to evaluate whether the information provided by impedance can influence clinical decision-making in patients with DES.

The above observations suggest that routine esophageal function testing with combined MII-EM may result in a new paradigm in defining esophageal motility abnormalities; distinguishing those associated with abnormal bolus transit compared to those showing only abnormal pressure (Figure 7). Overall, these results suggest that the bolus transit information obtained with combined MII-EM will clarify which patients with abnormal manometry actually have an esophageal function defect.

Outcome-based studies are needed to establish the prognostic values of combined MII-EM and establish the clinical utility of the additional information obtained with this form of testing. Future studies aim at clarifying whether combined MII-EM will be superior to traditional manometry in the esophageal function testing armamentarium, particularly in patients with non-obstructive dysphagia and in pre-operative testing for anti-reflux surgery.

**Combined Esophageal Impedance-pH Monitoring**

Combined MII-pH monitoring represents a shift in the reflux testing paradigm that was initiated by Spencer’s 1969 description of intrasophageal pH testing for GERD. Conventional pH monitoring relies on a rapid decline in intrasophageal pH to less than 4 as a marker for presence of gastric content in the esophagus, limiting its use in detecting gastroesophageal reflux (GER) episodes where pH fails to fall below this threshold. MII detects all types of GER episodes by retrograde progression of changes in intraluminal impedance, as the reflux episode advances from the stomach into the esophagus. The information from the pH electrode is used primarily to characterize the H+ concentration in the GER episodes and separate them into acid or non-acid by pre-established criteria.

The ability of combined MII-pH to detect and characterize non-acid GER represents an important advance for clinical testing of non-acid reflux. Previous techniques were developed in order to overcome the limitations of conventional pH testing in detecting GER episodes during which the pH is not below 4.

Bilirubin monitoring (Bilitec, Medtronic) requires the presence of bilirubin in the gastroesophageal refluxate in order to detect the presence of non-acid material in the esophagus. Studies involving simultaneous MII and bilirubin monitoring suggest that only 10% of non-acid reflux episodes contain bile. After ingestion of a radiolabeled meal, scintigraphy can also detect...
GER independent of the pH of the refluxate, although this technique is limited due to the continuous emptying of the tracer from the stomach and the need for radiation. Another method of detecting gastroesophageal reflux, independent of chemical composition, could be manometric monitoring with identification of transient lower esophageal sphincter relaxation and common cavity events, although this method would be quite challenging in the ambulatory setting.

From a patient perspective, combined MII-pH testing is no different from conventional pH testing. Combined MII-pH catheters have the same diameter as regular pH catheters (2.1 mm) and patients are instructed to keep a diary noting the times of meals, changes in body position, and symptoms. Catheters used for clinical MII-pH testing (Figure 8) are placed in reference to the manometrically defined proximal border of the lower esophageal sphincter (LES) and incorporate 4 impedance-measuring segments in the distal esophagus (3 cm, 5 cm, 7 cm, and 9 cm above the LES) and 2 segments in the proximal esophagus (15 cm and 17 cm above the LES). They also have an antimony esophageal pH sensor (5 cm above the LES) with an optional antimony gastric pH sensor (10 cm below the LES).

Combined MII-pH monitoring classifies GER episodes by their physical characteristics as liquid, gas, or mixed reflux events. A second classification is based on the pH characteristics of the refluxate. Traditionally, MII-detected episodes are classified into acid, non-acid, minor acidic, and acid re-reflux. An acid MII-GER event is an MII-detected reflux event, in which a drop of pH from greater than 4.0 to below 4.0 is noted (Figure 9a). Non-acid reflux is a MII-detected event during which the pH stays above 4.0 and does not drop more than 1 pH unit (Figure 9b). Minor acid reflux is an MII-detected reflux event during which pH stays above 4.0 but the pH drops more than 1 unit (Figure 9c). An acid re-reflux event occurs when intraesophageal pH is already below 4.0. It is detected by MII and the pH may or may not go further below 4.0 (Figure 9d).

A revision to this nomenclature has been proposed by a group of 11 esophageal experts after a workshop in Oporto, Portugal in 2002. The revised classification maintains the same criteria for acid reflux (drop in pH from above to below 4) and renames acid re-reflux as superimposed reflux (MII-detected reflux occurring while the esophageal pH is still below 4). Arguing that solutions with a pH between 4 and 7 are acidic by chemical criteria, the group proposed the term “weakly acidic” for MII-detected reflux episodes during which the pH is between 4 and 7 and the term “weakly alkaline” to episodes during which the pH does not drop below 7 (Table 1).

From a pragmatic point of view, we prefer a simplified
classification of gastroesophageal reflux detected by combined MII-pH monitoring. We consider an MII-detected reflux episode to be acid if the concomitantly measured intraesophageal pH nadir is below 4 or non-acid if the intraesophageal pH remains above 4.

Normal values for combined MII-pH monitoring have been established in a multicenter study in 60 healthy volunteers. Data in normal volunteers suggest that in the absence of acid-suppressive therapy, the vast majority of GER episodes are acidic, with nonacid GER episodes limited primarily to postprandial periods. Of particular interest in this study is the observation that the time intraesophageal pH is below 4 (detected by pH monitoring) is much longer than the time of actual acid bolus presence (detected by impedance) as underscoring the observation that acid clearance requires not only removal of the bolus but also neutralization of the mucosal acid. These data confirm prior scintigraphic-pH data reported by Helm and colleagues demonstrating that esophageal acid clearance time (assessed by pH) was much longer compared to the time a radiolabeled HCl bolus was present in the esophagus.

The most important role of combined MII-pH monitoring is likely in the evaluation of adult patients with residual symptoms while on acid suppressive therapy, patients with atypical reflux symptoms off acid suppressive therapy, and in infants (Table 2). The interest in nonacid GER testing in infants comes from the fact that acid output is decreased when compared with adults and feeding patterns (drinking milk or formula every 2–3 hours) facilitate long periods of time with the stomach full, thus buffering intragastric acid concentrations.

The role of monitoring patients with atypical GERD symptoms using combined MII-pH monitoring has been underscored in a recent study by Sifrim and associates. Monitoring 22 patients with persistent cough thought to be secondary to gastroesophageal reflux, they identified 10 patients (45%) with a positive temporal association (ie, positive symptom association probability [SAP]) between cough and reflux. In these patients off acid suppressive therapy, half had a positive SAP for cough and acid reflux, only 20% for cough and either acid reflux or weakly acidic reflux, and 30% for cough and weakly acidic reflux only. These results imply that in patients with chronic cough, gastroesophageal reflux with a pH above 4 can be the cause of symptoms and tests in these patients should examine these episodes.

The utility of monitoring patients with GERD symptoms on acid suppressive therapy is supported by the high prevalence of GERD symptoms and the popularity of empiric PPI trials (omeprazole test) to diagnose GERD. Although PPI therapy heals esophagitis in up to 90% of patients, data from a large study indicated that

### Table 1. Traditional and Revised Classification of Gastroesophageal Reflux Episodes

<table>
<thead>
<tr>
<th>pH Level</th>
<th>Traditional classification</th>
<th>Revised classification (Oporto Group 2002)</th>
</tr>
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<tbody>
<tr>
<td>Less than 4</td>
<td>Acid reflux</td>
<td>Acid reflux (MII-detected reflux starting while pH less than 4)</td>
</tr>
<tr>
<td>Between 4 and 7</td>
<td>Non-acid reflux (MII-detected reflux with pH change less than 1 unit)</td>
<td>Weakly acidic reflux</td>
</tr>
<tr>
<td>Greater than 7</td>
<td>Minor-acid reflux (MII detected reflux with pH above 4 and pH change greater than 1 unit)</td>
<td>Weakly alkaline reflux</td>
</tr>
</tbody>
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MII = multichannel intraluminal impedance.
up to 40% of patients with GERD were having persistent symptoms after 4 weeks of PPI therapy. Studies from our laboratory have shown that continuing symptoms while on acid-suppressive therapy are either associated with acid and non-acid GER episodes or not related to reflux episodes at all. Preliminary data from a multicenter study evaluating the relationship between residual symptoms on PPI therapy and acid and non-acid reflux suggest that persistent acid reflux is associated with symptoms in only 20% of patients on PPI therapy. In approximately 40% of patients, the residual symptoms are due to non-acid reflux whereas, in the remaining 40% of patients, the symptoms are not related to GER episodes. These percentages are dependent on the type (typical or atypical) of GERD symptoms. Combined MII-pH monitoring is an important addition to the clinical armamentarium for diagnosing and managing GERD. Since GER episodes are detected independently of their pH, combined MII-pH allows detection of all types of reflux events and thus provides information not only about their chemical (pH) composition but also about their physical properties (liquid, gas, mixed). By its ability to separate bolus clearance from acid clearance and identify acid re-reflux episodes, combined MII-pH improves our understanding regarding the mechanisms of long pH-detected acid reflux episodes.

The most important addition provided by this method is the ability to identify the mechanism of residual GERD symptoms on acid suppressive therapy as due to persistent acid reflux, nonacid reflux, or no reflux. In our experience, combined MII-pH monitoring has changed the diagnostic algorithm for GERD (Figure 10).

References