Esophageal multichannel intraluminal impedance testing

Authors
Radu Tutuian, MD
Donald O Castell, MD

Section Editor
Nicholas J Talley, MD, PhD

Deputy Editor
Shilpa Grover, MD, MPH

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Literature review current through: Sep 2014. | **This topic last updated:** Jan 29, 2013.

INTRODUCTION — Multichannel intraluminal impedance (MII) is a new technique designed to detect intraluminal bolus movement without the use of radiation. It is generally performed in combination with manometry or pH testing. When combined with manometry, it provides information on the functional (ie, bolus transit) component of manometrically detected contractions. When combined with pH testing, it allows for detection of gastroesophageal reflux independent of pH (ie, both acid and non-acid reflux).

PRINCIPLES OF MII — Impedance testing depends upon measurement of changes in resistance (in Ohms) to alternating electrical current when a bolus passes by a pair of metallic rings mounted on a catheter. In an empty tubular organ (ie, esophagus or small intestine) the electrical current between the two rings is conducted by the few ions present in and on the esophageal mucosa. Liquid containing boluses with an increased number of ions have a higher conductivity and when entering the impedance measuring segment will lower the impedance to a nadir value.

The impedance stays at its nadir as long as the bolus is present in the segment, returning to baseline once the bolus is cleared by a contraction. The contraction produces a slight increase in impedance above the baseline due to a decrease in luminal cross-section. Gas passing transiently by the impedance measuring segments will produce a rapid rise in the impedance since it has poor electrical conductance.

Measuring impedance at multiple sites (multichannel) allows for determination of direction of bolus movement based upon temporal differences in bolus entry and exit (ie, bolus entries progressing from proximal to distal indicate antegrade bolus movement while bolus entries progressing from distal to proximal indicate retrograde bolus movement) (waveform 1). Combined with manometry (multichannel intraluminal impedance and manometry; MII-EM) it provides information about both pressures and bolus transit within the esophagus. Combined with pH (multichannel intraluminal impedance and pH; MII-pH) it permits detection of both acid and non-acid gastroesophageal reflux.

The United States Food and Drug Administration approved MII to detect intraluminal bolus movement in July 2002. Combined MII-EM is approved for esophageal function testing and combined MII-pH for gastroesophageal reflux monitoring (Sandhill Scientific Inc, Highlands Ranch, CO, USA).

COMBINED MULTICHANNEL INTRALUMINAL IMPEDANCE AND MANOMETRY (MII-EM)

Indications — The indications for MII-EM are similar to those for esophageal manometry: evaluation of patients with dysphagia, non-cardiac chest pain, heartburn/regurgitation, preoperative evaluation before anti-reflux surgery or endoscopic anti-reflux procedures and location of the LES prior to pH catheter placement. One study suggested better sensitivity compared with standard manometry for detection of motility disturbances in patients with non-obstructive dysphagia [1].

In one study, dysphagia was more common in 158 patients with normal manometry and abnormal bolus transit on MII-

EM testing compared with 146 patients with normal manometry and normal bolus transit (23 versus 10 percent). The authors suggested that combined MII-EM is more sensitive in detecting an esophageal abnormality than is standard manometry in dysphagia patients [2].

Ongoing studies are helping to determine whether there will be a role in diagnosis of extra-esophageal disorders related to GERD, such as chronic cough [3].

Procedure — Patients are asked to fast for four to six hours, after which the combined MII-EM catheter is inserted transnasally through the esophagus into the stomach. The procedure is performed in an outpatient setting. The lower esophageal sphincter (LES) is located by stationary pull-through technique and the most distal sensor is placed in the high-pressure zone of the LES.

The design of the catheter determines the location of the pressure and impedance-measuring segment. The currently available 9-channel esophageal function testing catheter (Sandhill Scientific Inc, Highlands Ranch, CO) has five pressure sensors 5 cm apart and four impedance measuring segments straddling the four proximal pressure sensors, allowing pressure measurements in the LES, and at 5, 10, 15, and 20 cm above the LES. Impedance measuring segments are centered at 5, 10, 15, and 20 cm above the LES.

After successful catheter placement, 10 liquid (ie, 0.9 percent normal saline) and 10 viscous (ie, standardized viscous solution; Sandhill Scientific Inc, Highlands Ranch, CO) swallows are given, each 30 seconds apart. Saline is preferred over plain water since it has a standardized ionic concentration allowing reliable identification of bolus presence by impedance. The impedance of water can vary depending upon its source, leading to potential impedance artifacts.

Data analysis — Data analysis is performed using dedicated software (BioView Analysis, Sandhill, Scientific Inc, Highlands Ranch, CO).

Swallows are classified by manometry as:

- Normal, if contraction amplitudes at 5 and 10 cm above the LES are each greater than or equal to 30 mmHg and distal onset velocity is less than 8 cm/second
- Ineffective, if either of the contraction amplitudes at 5 and 10 cm above the LES is less than 30 mmHg (this includes contractions that have been defined as "poorly transmitted" or "not transmitted" in some reports)
- Simultaneous, if contraction amplitudes at 5 and 10 cm above the LES are each greater or equal to 30 mmHg and distal onset velocity is greater than 8 cm/second

Swallows are classified by MII as showing:

- Complete bolus transit, if bolus entry occurs at the most proximal site (20 cm above LES) and bolus exit points are recorded in all three distal impedance-measuring sites (ie, 15, 10, and 5 cm above the LES)
- Incomplete bolus transit if bolus exit is not identified at any one of the three distal impedance measuring sites

The interpretation of the manometric information is based upon published criteria [4].

- Normal esophageal manometry is defined as not more than 40 percent ineffective and not more than 10 percent simultaneous swallows, an average distal esophageal amplitude (DEA) <220 mmHg and normal LES resting and residual pressures
- Achalasia is defined by absent esophageal body peristalsis and, if present, poorly relaxing LES
- Scleroderma is defined based upon an appropriate clinical diagnosis and confirmed by low amplitude or absent contractions in the distal esophagus with or without a low LES pressure

- Distal esophageal spasm is defined as 20 percent or more simultaneous contractions
- Ineffective esophageal motility is defined as 50 percent or more swallows with contraction amplitude less than 30 mmHg in either of the two distal sites located at 5 and 10 cm above the LES
- Nutcracker esophagus is defined as normal peristalsis of the esophageal body with DEA exceeding 220 mmHg
- Poorly relaxing LES is defined as average LES residual pressure exceeding 8 mmHg associated with normal esophageal body contractions
- Hypertensive LES is defined as LES resting pressure exceeding 45 mmHg with normal esophageal body contractions
- Hypotensive LES is defined as LES resting pressure below 10 mmHg with normal esophageal body contractions

Esophageal transit abnormalities are considered to be present if 30 percent or more of liquid swallows have incomplete bolus transit or if 40 percent or more of viscous swallows have incomplete bolus transit. These values are based upon data from 43 healthy volunteers [1]. Studies in patients with esophageal motility abnormalities indicate that no patients with achalasia or scleroderma have normal bolus transit, while almost all (ie, 95 percent or more) patients with normal manometry, nutcracker esophagus, or isolated lower esophageal sphincter (LES) abnormalities (ie, hypertensive LES, hypotensive LES or poorly relaxing LES) have normal bolus transit. Approximately 50 percent of patients with ineffective esophageal motility (IEM) or distal esophageal spasm (DES) have normal liquid bolus transit [5]. A study using relatively sensitive criteria to define abnormal bolus transit (ie, abnormal bolus transit for liquid and/or viscous swallows) in patients with non-obstructive dysphagia found abnormal bolus transit in 35 percent of patients with otherwise normal manometry, 66 percent of those with DES, 85 percent of those with IEM and 100 percent of patients with achalasia [6].

Combined MII-EM helps clarify the functional defect in patients with manometrically defined ineffective esophageal motility (IEM) and distal esophageal spasm (DES). We found that the current criteria used to distinguish manometrically normal from IEM were only 85 percent sensitive and 65 percent specific in a group of 70 patients who we evaluated with MII-EM [7]. Based upon liquid and viscous swallows, approximately one-third of patients had a mild functional defect (ie, normal bolus transit for both liquid and viscous), while another third had a moderate defect (ie, abnormal bolus transit for either liquid or viscous), and the remaining third had a severe defect (ie, abnormal bolus transit for both liquid and viscous).

Studies from our laboratory using combined multichannel intraluminal impedance and manometry (MII-EM) to evaluate esophageal peristalsis and bolus transit in 71 patients with DES indicate that approximately half of patients who have manometric criteria of DES have normal bolus transit for both liquid and viscous swallows (ie, no functional defect). About 25 percent of DES patients have abnormal bolus transit for both liquid and viscous swallows (ie, a severe functional defect), while the remainder have abnormal bolus transit for either liquid or viscous swallows (ie, a moderate functional defect) [8].

Another group described the results of combined impedance-manometry testing in 80 patients who underwent laparoscopic Nissen fundoplication [9]. While manometric findings were similar in patients with and without dysphagia (impaired peristalsis 17 versus 14 percent), MII found more bolus transit abnormalities in patients with dysphagia than in those without dysphagia (62 versus 32 percent). These findings suggest that combined MII-EM can identify esophageal function abnormalities in patients with post-operative dysphagia missed by conventional manometry.

Functional information provided by such analysis allows for categorization of transit abnormalities into those with a pressure-only defect and those with a pressure and bolus transit defect (table 1).

Combined impedance-manometry testing can be used to quantify esophageal function (peristalsis and bolus transit) during unrestricted swallowing as it occurs physiologically during meal consumption. One study, for example, quantified

the passage of a food bolus through various levels in the esophagus in 10 healthy volunteers [10]. The volunteers consumed two pieces of toast and 2 ounces of liquids. The authors observed that liquids and solids were present in the esophagus for less than 33 percent of the duration of meal ingestion.

COMBINED MULTICHANNEL INTRALUMINAL IMPEDANCE AND PH (MII-PH) — Another FDA-approved application of multichannel intraluminal impedance is gastroesophageal reflux monitoring using combined MII-pH (Sandhill Scientific Inc., Highlands Ranch, CO, USA). Reflux is detected by impedance and classified as acid or non-acid depending upon the concomitant changes in the intraesophageal pH. A consensus statement prepared by an international panel of esophageal experts considered impedance monitoring currently the best method that can achieve high sensitivity for detecting all types of reflux episodes [11].

Indications — Assuming that the results would alter clinical management, the indications for combined MII-pH studies are to quantify and characterize gastroesophageal reflux (GER), especially in patients with persistent symptoms on acid-suppressive therapy who have normal endoscopic findings [12].

For the detection and quantification of GER in patients off acid suppressive therapy, conventional pH testing (using catheter or catheter-free systems) should be sufficient, since non-acid reflux is uncommon in patients off acid-suppressive therapy. However, this conclusion may not apply to the post postprandial period or to patients who do not produce acid due to prior gastrectomy or atrophic gastritis.

Given the popularity of empiric trials of PPIs, we suggest that patients be on high dose acid suppressive therapy (ie, at least a PPI twice daily before meals) for at least one week before combined MII-pH testing.

Other indications for combined MII-pH studies are evolving. The following benefits have been noted with combined MII-pH studies in different reports:

- Facilitated diagnosis of reflux in patients with refractory GER disease on a PPI [13]. Efficacy in this setting was demonstrated in a study of 39 patients with refractory reflux: 14 had abnormal impedance testing while on PPI therapy, 13 of whom had persistent acid reflux off therapy. Thus, an abnormal impedance test while on therapy was a strong predictor of acid reflux off therapy. In contrast, normal impedance testing on therapy did not exclude acid reflux off therapy.
- Facilitated diagnosis of reflux compared with pH data alone in patients in whom a PPI was temporarily discontinued [14].
- Improved detection of laryngopharyngeal reflux and microaspiration [15,16].

Procedure — Combined MII-pH testing is similar to pH testing. Patients are asked to fast for four to six hours prior to the probe insertion. Patients taking acid-suppressive therapy should be instructed to take the medications as prescribed, even on the day of testing. The combined MII-pH probe is placed transnasally into the esophagus. Currently available probes are 2.1 mm in diameter (similar to conventional pH probes) and allow for pH sensors to be placed 5 cm above the LES and 10 cm below the LES with impedance measuring segments at 3, 5, 7 and 9 cm above the LES in the distal esophagus and at 15 and 17 cm above the LES in the proximal esophagus (figure 1). Patients are instructed to have a "usual" day and are provided a diary to record the time and content of meals, time of upright and recumbent periods, time of administration of acid-suppressive medication, and time of symptoms. We encourage patients to induce as many symptoms as they can by either ingesting foods and/or doing activities known to produce symptoms. The following day the patient returns the logger and diary and data are downloaded (Zephyr, Sandhill, Scientific Inc, Highlands Ranch, CO).

Data analysis — Data analysis is performed using dedicated software (BioView GER Analysis, Sandhill, Scientific Inc, Highlands Ranch, CO).

GER composition and proximal extent — Reflux episodes can be classified by MII as containing gas, liquid, or both, based upon different impedance patterns. Air conducts electricity poorly and therefore has very high impedance, whereas liquid gastric contents have low impedance. Mixed reflux events are a combination of both a liquid and gas pattern. The proximal extent of a reflux event is defined by the most proximal impedance measuring segment reached by the liquid component of the reflux episode. Gas reflux events are not assigned a proximal extent since they typically penetrate the UES and are eliminated.

GER content: Acid, non-acid, weakly acidic, weakly alkaline reflux — An acid reflux event is defined as an event during which there is a drop of pH to below 4.0. Non-acid reflux is defined as an event during which the pH stays above 4.0 (figure 2). Acknowledging that solutions with pH between 4.0 and 7.0 are acidic from a chemist point of view, some investigators prefer using the term "weakly acidic" for reflux episodes with pH 4.0 to 7.0, and the term "weakly alkaline" for reflux episodes with pH >7.0 [11]. Since weakly alkaline reflux episodes (pH >7.0) are rare, from a practical point of view the terms "weakly acidic" and "non-acid" describe the same event, ie, reflux episodes with pH >4.0.

Combined MII-pH parameters — Combined MII-pH is a dual modality technique for detecting GER. Its parameters are more complex than those used during traditional 24 hour ambulatory pH monitoring (ie, the number of episodes and percent time pH <4 identified). In addition to these two pH-parameters, combined MII-pH defines the number of MII-GER episodes as the total number of MII-detected episodes.

- Refluxate presence time is defined as the total amount of liquid containing MII refluxate presence time (absolute or percent of the study period) detected by the impedance-measuring segment located at 5 cm above the LES
- Refluxate clearance time is defined as the average duration of liquid containing MII-refluxate presence at 5 cm above the LES

All of the above mentioned parameters are further separated into acid and non-acid based upon the pH changes recorded at the time when the reflux occurred. According to the position of the subject at the time the GER occurs, these parameters are further separated into upright and recumbent.

Overall study interpretation — Overall study interpretation was based initially upon normative data described in a study of 60 healthy volunteers [17]. Subsequent studies have found that postprandial gastroesophageal reflux data with impedance monitoring are as reproducible as when assessed with pH monitoring [18]. In the postprandial period, acid suppressive therapy primarily changes the ratio of acid versus non-acid reflux episodes with less effect on the total number of episodes [19].

Studies evaluating the number of acid and non-acid reflux episodes in healthy volunteers monitored on PPIs twice daily indicate that acid suppressive therapy decreases the total number of reflux episodes, presumably by reducing the total amount of gastric secretion [20,21]. As a result, different normal values should be used when interpreting the total number of reflux episodes in patients "off" and "on" acid suppressive therapy (table 2).

Influence on management — Accumulating studies have evaluated the role of impedance testing in evaluation of patients with esophageal symptoms, particularly in those who continue to have symptoms despite acid suppression. As a general rule, these have demonstrated that impedance testing clarifies the relationships among symptoms, acid and non-acid reflux [3,22-29].

Patients with persistent symptoms despite PPIs in particular represent a diagnostic dilemma during conventional pH testing. Combined MII-pH helps clarify the association of symptoms with reflux events, and has demonstrated that about one-half of patients with persistent symptoms on therapy do not have a temporal correlation between their symptoms and any type of reflux. In addition, about 40 percent of patients with persistent symptoms on PPI therapy have a temporal association between their symptoms and reflux, primarily of the non-acid type.

However, whether the improved understanding of symptoms to reflux and non-reflux events translates into better health

outcomes has not yet been well-established.

The following are illustrative of the range of findings:

- A multicenter collaborative study including 168 patients found that only 11 percent of patients with persistent symptoms on acid-suppressive therapy had symptoms related to continued acid reflux [22]. The other 89 percent had symptoms associated either with non-acid reflux or not associated with any type of GER.
- Up to one-half of patients with persistent typical gastroesophageal reflux disease (GERD) symptoms on PPI therapy had symptoms associated with non-acid reflux in another report [22], while in another study, acid reflux was associated with symptoms in only 5 percent of patients [23]. A third report involving 150 patients classified as having nonerosive reflux disease found that a substantial proportion of patients had symptoms attributable to non-acid reflux [29]. Reclassifying those with symptomatic non-acid reflux as having a hypersensitive esophagus reduced the number of patients classified as having functional heartburn from 43 to 26 percent.
- A study of 125 patients with persistent symptoms despite PPIs demonstrated that most reflux episodes were asymptomatic [28]. However, reflux episodes extending proximally and having a mixed (liquid-gas) composition were significantly associated with symptoms, irrespective of whether the pH was acidic or non-acidic.
- Another study evaluating 22 patients with chronic cough off PPI therapy found that 10 patients (45 percent) had a positive symptom association between cough and reflux [3]. Symptoms were associated with non-acid reflux, which was detectable only by impedance-pH monitoring.
- Our group evaluated 50 patients with persistent cough while on a PPI and found an association between cough and reflux in 13 patients (26 percent) [24]. The clinical relevance of these findings was underscored by the clinical improvement in six patients with a positive association between cough and reflux who underwent laparoscopic fundoplication.
- A study in 30 patients with typical GERD symptoms found a similar total number of impedance detected reflux episodes while patients were off (73 ± 33) or on (69 ± 35) acid suppressive therapy [30]. This underscores the concept that PPI therapy changes the pH of the refluxate but has no influence on the frequency of gastroesophageal reflux episodes. A positive symptom association (SAP) was found in 15 out of 28 (54 percent) patients reporting symptoms while monitored off therapy and in 11 out of 23 (48 percent) patients reporting symptoms while monitored on therapy.
- A study in a cohort of 19 patients who underwent anti-reflux surgery based upon the results of MII-pH monitoring found that 17 of 18 patients with documented positive symptom association between reflux (acid and non-acid) reported no symptoms at a median follow-up time of 14 months after surgery [25]. These results indicate that MII-pH monitoring on therapy helps identify patients with persistent typical and atypical reflux symptoms who may benefit from anti-reflux surgery.

SUMMARY AND RECOMMENDATIONS

- Measuring impedance at multiple sites (multichannel) allows for determination of direction of bolus movement based upon temporal differences in bolus entry and exit (ie, bolus entries progressing from proximal to distal indicate antegrade bolus movement while bolus entries progressing from distal to proximal indicate retrograde bolus movement) (waveform 1). (See 'Principles of MII' above.)
- Combined MII-EM offers the opportunity to simultaneously evaluate esophageal contractions and bolus transit without the use of radiation. Some of the findings challenge current existing criteria that define effectiveness of esophageal body function. Future studies are warranted to evaluate the prognostic values of pressure and bolus transit abnormalities and also to continue to incorporate high resolution manometry with impedance

measurements. (See 'Combined multichannel intraluminal impedance and pH (MII-pH)' above.)

- Combined MII-pH testing brings a shift in GER testing paradigm. In MII-pH studies reflux presence, distribution and clearing is primarily detected by MII and simply characterized as acid versus non-acid based upon pH change and as liquid, gas, or mixed based upon MII. MII determines refluxate clearance time while pH measures acid clearance time. MII-pH has become an important clinical tool, particularly to assess gastroesophageal reflux in the postprandial period, in patients with persistent symptoms on proton pump inhibitor (PPI) therapy, and those with atypical symptoms. In these situations it has great potential to direct therapy to additional pharmacologic approaches, surgery, or perhaps even endoscopic modification of reflux. (See 'Combined multichannel intraluminal impedance and pH (MII-pH)' above and "Approach to refractory gastroesophageal reflux disease in adults" and "Surgical management of gastroesophageal reflux in adults" and "Radiofrequency treatment for gastroesophageal reflux disease".)

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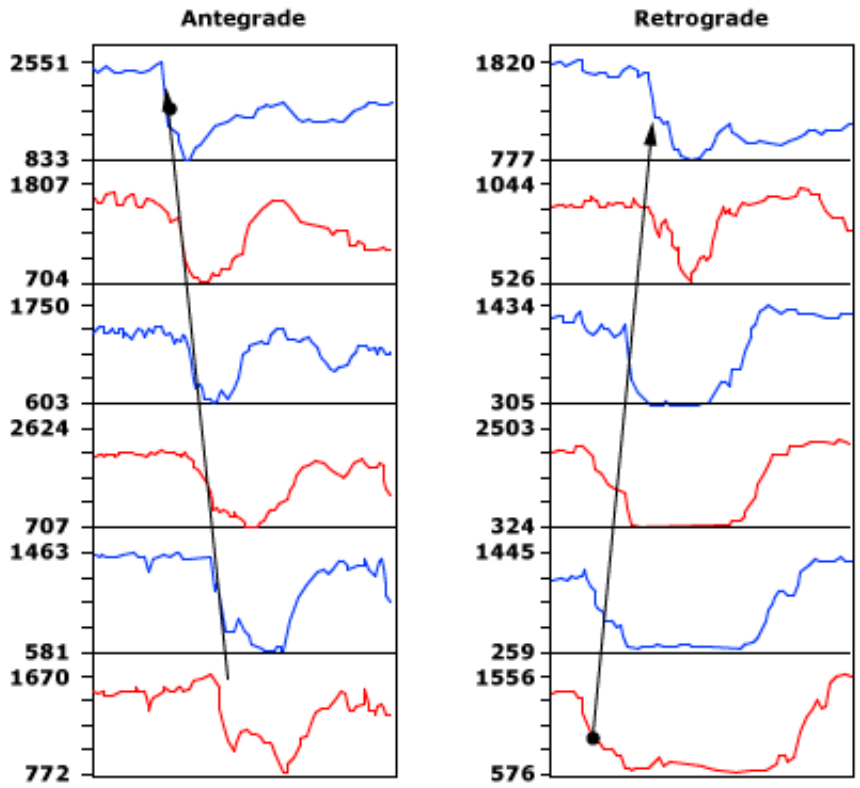
Topic 2248 Version 8.0

GRAPHICS

MI detected bolus movement



Changes in intraluminal impedance during swallowing and reflux. A drop in impedance identifies bolus entry in a segment followed by a recovery once the bolus exits the impedance-measuring segment. Changes in impedance progressing from proximal to distally indicate antegrade bolus movement as seen during swallowing while changes in impedance progressing distally to proximally indicate retrograde bolus movement as seen during reflux.

Courtesy of Radu Tutuian, MD and Donald O Castell, MD.

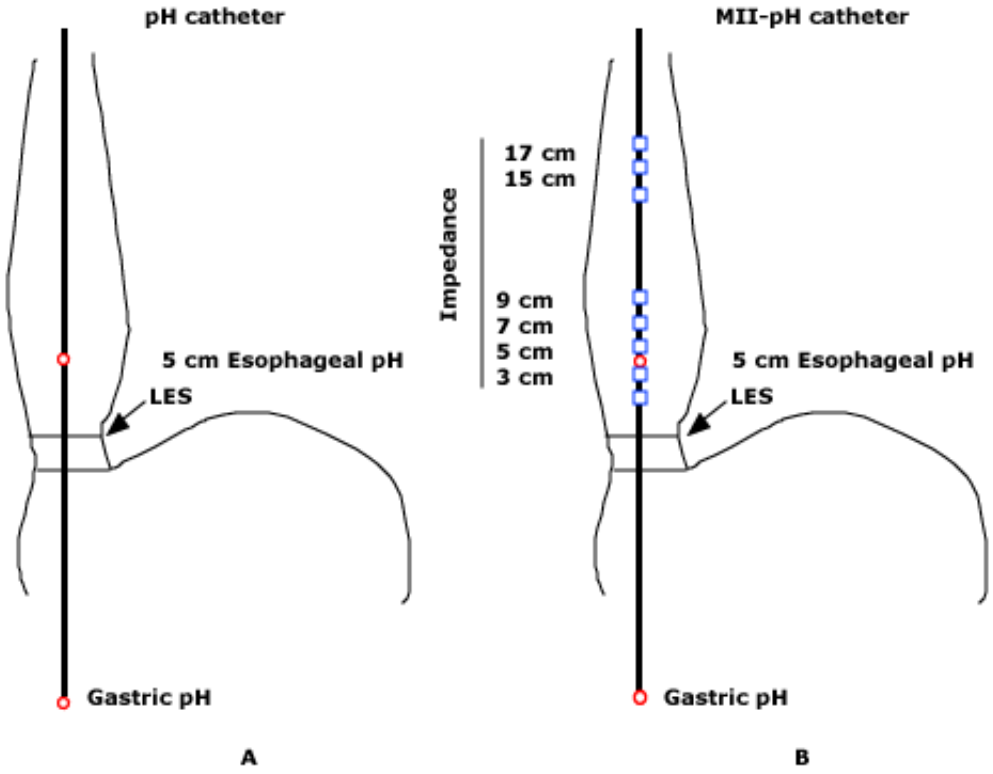
Graphic 56477 Version 2.0

Esophageal motility abnormalities

Abnormal pressure and transit
Achalasia
Scleroderma
Ineffective esophageal motility
Distal esophageal spasm
Abnormal pressure only
Nutcracker esophagus
Hypertensive LES
Hypotensive LES
Poorly relaxing LES

Graphic 81342 Version 1.0

(A) conventional pH catheter (diameter 2.1 mm) used to monitor gastroesophageal reflux and intragastric pH, (B) multi-channel intraluminal impedance-pH catheter (diameter 2.1 mm) with impedance electrodes (4 mm in length) set in pairs at 2-cm intervals

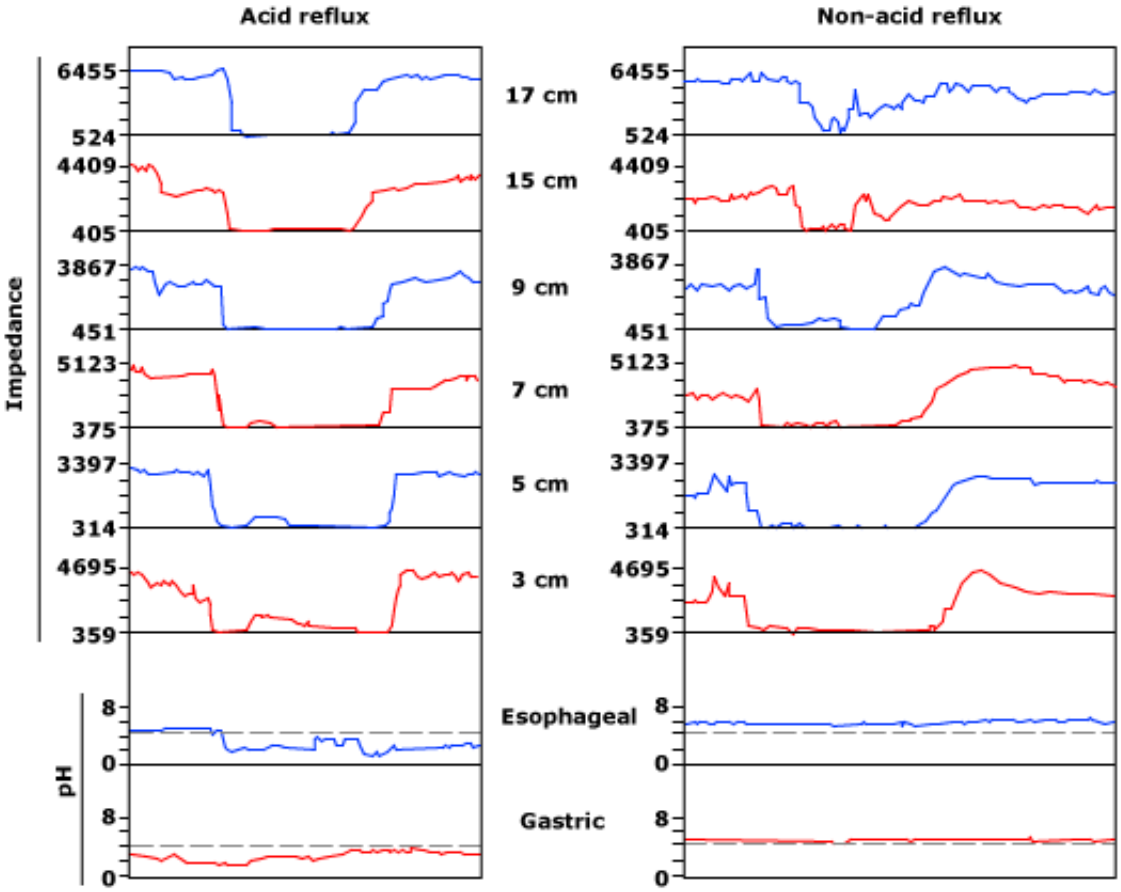


This allows for six impedance rings and one pH electrode in the esophagus and a second pH electrode in the stomach. The pH sensor is placed 5 cm above the LES and gastric pH at 10 cm below the LES.

Courtesy of Radu Tutuian, MD and Donald O Castell, MD.

Graphic 68998 Version 1.0

Acid and non-acid reflux identified by combined MII-pH monitoring



Reflux is identified by changes in impedance progressing distally to proximally as liquid advances from the stomach into the esophagus. Information from the pH electrode is used to classify reflux as acid (ie, pH drops from above to below 4) or non-acid (ie, pH remains above 4).

Courtesy of Radu Tutuian, MD and Donald O Castell, MD.

Graphic 55868 Version 1.0

Normal values for combined impedance-pH monitoring based on 95th percentile data in healthy volunteers off and on acid suppressive therapy

		Off therapy (N = 60)	On therapy (PPI twice daily) (N = 20)
Esophageal pH data			
Percent time pH <4	Total	6.7 percent	1.3 percent
	Upright	9.7 percent	2.2 percent
	Recumbent	2.1 percent	0.0 percent
Esophageal MII-data			
Nr. reflux episodes	Total	73	48
	Acid	55	12
	Non-acid	27	44

Data from:

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Graphic 56522 Version 1.0

Disclosures

Disclosures: **Radu Tutuian, MD** Speaker's Bureau: MMS International; Sandhill Scientific [Reflux testing, esophageal manometry (MMS Ohmega, Persaflex catheter; Sleuth monitor; ZepHiR monitor; MII-pH catheter)]. Consultant/Advisory Boards: Abbott; Allmiral; Sucampo [Constipation (lubiprostone, linaclotide)]. **Donald O Castell, MD** Consultant/Advisory Boards: Sandhill Scientific (esophageal testing equipment). **Nicholas J Talley, MD, PhD** Grant/Research support: Abbott Pharmaceuticals [IBS (pancreatic enzymes)]; Datapharm Australia [Constipation (kivea)]; Forest [FDTT NIH Funded Trial Medication (SSRI escitalopram)]; Ironwood/Forest/Astra Zeneca [IBS Constipation (linaclotide)]; Janssen [Constipation (prucalopride)]; Pfizer [IBS (pregabalin)]; Prometheus [IBS (no medication)]; Rome III Study [GI disorders (no medication)]; Salix Study [SIBO (rifaximin)]. Consultant: Danone [IBS (probiotics)]; Entera health [IBS (enteropathy and immunoglobulins)]; Forest [Functional dyspepsia (linaclotide)]; gIcare [Endoscopy (analgesia)]; Prometheus [IBS) (no medication)]. Patents: Biomarkers for IBS. **Shilpa Grover, MD, MPH** Employee of UpToDate, Inc.

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