

Esophageal function testing

The ASGE Technology Committee provides reviews of existing, new or emerging endoscopic technologies that have an impact on the practice of GI endoscopy. Evidence-based methodology is used, performing a MEDLINE literature search to identify pertinent clinical studies on the topic and a MAUDE (U.S. Food and Drug Administration Center for Devices and Radiological Health) database search to identify the reported complications of a given technology. Both are supplemented by accessing the “related articles” feature of PubMed and by scrutinizing pertinent references cited by the identified studies. Controlled clinical trials are emphasized, but in many cases, data from randomized, controlled trials are lacking. In such cases, large case series, preliminary clinical studies, and expert opinions are used. Technical data are gathered from traditional and Web-based publications, proprietary publications, and informal communications with pertinent vendors.

Technology Status Evaluation Reports are drafted by 1 or 2 members of the ASGE Technology Committee, reviewed and edited by the committee as a whole, and approved by the Governing Board of the ASGE. When financial guidance is indicated, the most recent coding data and list prices at the time of publication are provided. For this review, the MEDLINE database was searched through February 2011 for articles related to endoscopy by using the key words esophageal manometry, high-resolution manometry, dysphagia, achalasia, diffuse esophageal spasm, reflux, impedance, MII, pH testing, and gastroesophageal reflux disease.

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BACKGROUND

Esophageal function testing can be a useful adjunct for the evaluation of upper GI tract symptoms. The current

technology includes conventional and high-resolution manometry (HRM), and multichannel intraluminal impedance (MII) and pH monitoring, which measure esophageal intraluminal pressure, bolus transit, and pH, respectively. These data can be useful in the diagnosis of esophageal disease in patients presenting with heartburn, dysphagia, noncardiac chest pain, and extraesophageal symptoms such as cough and globus.^{1,2} This review summarizes the current technology available for the evaluation of esophageal function with manometry and impedance. A thorough review of pH testing is available in a separate report.³

PART I: ESOPHAGEAL MANOMETRY

Technology under review

Clinical application of esophageal manometry began in the 1940s with rudimentary setups of water-filled balloons and has since evolved into a more complex array of catheters, transducers, data recorders/computers, and analysis software. Today, both conventional manometry and HRM systems are available, with the main distinction between the 2 being the number of pressure sensors found on the esophageal catheters. Conventional manometry uses catheters with 4 to 8 pressure sensors, whereas HRM catheters have a higher number of pressure sensors (available in 20-36 channels) separated by shorter intervals. The techniques for data acquisition are similar, but HRM allows more versatility in data analysis.⁴ As such, HRM systems have been readily adopted and are now the predominant system. This report therefore focuses on HRM.

Main components

The esophageal manometry catheter is a long, flexible tube that is placed in the patient's esophagus with the distal tip lying in the stomach. The catheters can be made of a variety of plastic materials, most frequently polyvinyl chloride or silicone. The tip is slightly curved and may include a weighted distal metal tip to facilitate passage into the stomach. The compliance of some catheters changes with alterations in temperature, which may assist placement. Catheters are available in a variety of configurations, with diameters ranging from 2.7 to 4.7 mm and the number of sensors ranging from 4 to 36 (Table 1). There are 2 types of manometry catheters: water perfusion and solid state.

TABLE 1. Esophageal manometry systems

Company	System	Catheter compatibility	Catheter specs	Cost
Medical Measurements Systems	Solar GI (conventional), Solar GI HRM (HRM and HRIM); both systems are customizable	Compatible with a variety of water-perfused and solid-state catheters for conventional manometry, HRM, and HRIM	Depending on configuration	\$35,000-\$55,000
Sandhill Scientific	InSIGHT G3	HRM/impedance	32 pressure (4 sensor circumferential)/16 impedance	\$57,900
Sierra Scientific	ManoScan 360	ManoScan catheter: HRM	36 pressure (12-sensor circumferential)	\$52,900
	ManoScan Z	ManoScan Z catheter: HRM/impedance	36 pressure (12-sensor-circumferential)/18 impedance	\$62,000
	ManoScan 3D	ManoScan 3D catheter: HRM with 3D	32 HRM (12-sensor circumferential)/12 high definition	\$78,900

HRM, High-resolution manometry; HRIM, high-resolution impedance manometry; 3D, 3-dimensional.

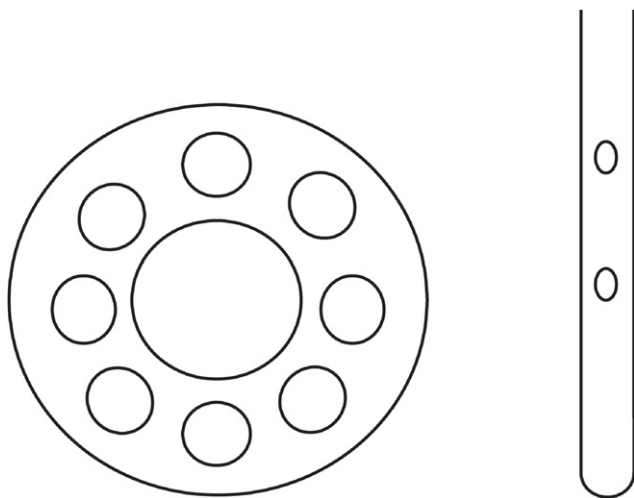


Figure 1. Cross-sectional and longitudinal view of a water-perfusion catheter.

The water-perfusion catheter contains multiple capillary tubes running longitudinally within it. The distal ends of the capillary tubes terminate at orifices that are oriented radially to the catheter tube (Fig. 1). The number and location of these orifices vary among catheter type and manufacturer. Some catheters have a separate central lumen that allows placement over a stylet or wire. Some manufacturers offer the option of customizable catheters (Arndorfer Inc, Greendale, Wisc; Mui Scientific [formerly Dentslevel], Mississauga, Ontario, Canada; Medical Management Systems, Dover, NH). The proximal ends of the capillary tubes extend beyond the catheter outside of the patient and are connected to external transducers. These

transducers are connected to a water-perfusion pump and a data recorder/computer.

The perfusion pump continuously infuses sterile water through the catheter. The pump is connected to a medical air outlet, an electric air compressor, or a tank of compressed nitrogen, which pressurizes water stored in a separate reservoir. Gauges display the levels of pressure in the gas compressor and water reservoir. The pressure can be adjusted by a manual regulator. The pressurized water in the reservoir is infused through the intracapillary tubes within the esophageal catheter. Pressure changes generated by the esophagus or lower esophageal sphincter (LES) transmitted via the radial ports, through the capillary tubes, and back to the external transducers and data recorder.

The solid-state catheter does not require the use of a water or a perfusion pump. The apparatus contains internal microtransducers composed of either metal diaphragm strain gauges or piezoresistive silicon chips. They have a pressure-sensitive surface as small as 1 mm², allowing an increased number of sensors along the catheter length. Esophageal pressure changes detected by these transducers are transmitted to the data recorder via a solid-state interface. The transducers can detect very rapid changes in frequency, enabling superior evaluation of the upper esophageal sphincter (UES) and pharynx compared with water-perfusion catheters.^{1,5} Solid-state catheters have either unidirectional or circumferential transducers. The unidirectional transducers are capable of measuring pressure from only 1 direction, whereas the circumferential transducers measure pressure from different sides and average the values.⁶ The function of the latter is advantageous for

TABLE 2. Criteria for diagnosing esophageal motility abnormalities^{73,74}

Functional defect	Diagnosis	Manometric findings
Aperistalsis	Achalasia	Absent distal peristalsis; increased LES pressure (>45 mm Hg); incomplete LES relaxation
Uncoordinated motility	DES	≥20% simultaneous contractions; repetitive contractions (>3 peaks); prolonged duration of contractions; incomplete LES relaxation
Hypercontractile	Nutcracker esophagus	Increased amplitude (>180 mm Hg); increased peristaltic duration
	Hypertensive LES	Resting LES pressure >45 mm Hg; incomplete LES relaxation
Hypocontractile	IEM	>30% nontransmitted peristalsis; peristaltic amplitude <30 mm Hg
	Hypotensive LES	Resting LES pressure <10 mm Hg

LES, Lower esophageal sphincter; DES, diffuse esophageal spasm; IEM, ineffective esophageal motility.

the assessment of intrasphincteric pressures where muscular regions are asymmetrical.

The final component of esophageal manometry is data recording and analysis. Dedicated software converts pressure recordings into visual format consisting of line tracings and topographic maps. The layout, capabilities, and special features of the software vary among manufacturers (Sandhill Scientific, Inc, Highlands Ranch, Colo; Sierra Scientific Instruments [of Given Imaging], Los Angeles Calif; Medical Management Systems). Although automated analysis is provided by the software, it does not replace interpretation by a clinician.

Technique

During manometry, pressures are measured within the esophageal body and at the LES. UES amplitude measurement may be performed for the evaluation of specific pharyngeal disorders. Diagnostic criteria for motility disorders are presented in Table 2.

Manometry catheters can be inserted transnasally or transorally. The transnasal route is preferred because of better tolerability and fewer recording artifacts.^{1,7} The tube is advanced until catheter markings and pressure tracings indicate that the distal tip is positioned in the stomach.

The large number of sensors in HRM technology provides more esophageal pressure recordings compared with conventional manometry. This allows LES and esophageal pressure measurements to be obtained with the catheter fixed in 1 location, obviating the need for pull-throughs, repositioning of the catheter, or the use of a sleeve sensor for LES measurement. A specialized HRM computer software analysis can create a virtual sleeve (eSleeve, Sierra Scientific; vSleeve, Medical Measurement Systems), which detects pressure across a span of 5 to 6 adjacent sensors on the distal catheter.

The data obtained via HRM can be incorporated into visual representations that may facilitate interpretation.

Translation of data into surface or contour plots, called high-resolution esophageal pressure topography, depicts pressure information in an intuitive manner, with amplitudes being represented by concentric circles or color gradients^{8,9} (Fig. 2). Three-dimensional HRM is an emerging technology that provides a digitally created 3-dimensional image of the esophagus. It may be helpful when assessing the UES and LES, which have asymmetrical muscular anatomy.

Some manufacturers have HRM catheters that also have the ability to perform simultaneous impedance testing during the manometry examination (Solar HRIM, Medical Measurement Systems; InSIGHT G3, Sandhill Scientific; ManoScan Z, Sierra Scientific). These are discussed in Part II of this report.

Ease of use and tolerability

The optimal performance of manometry requires accurate data acquisition and interpretation. In 1 study in which conventional manometry was used, interobserver agreement for the extremes of motility diagnoses (eg, normal and achalasia) was good at all levels of experience ($\kappa = 0.66-0.71$).¹⁰ However, for other motility disorders (eg, nutcracker esophagus, hypertensive and hypotensive LES, diffuse esophageal spasm), interobserver agreement was poor, even among experienced providers ($\kappa = 0.35$). HRM may be easier to perform and interpret than conventional manometry. The mean procedure time is decreased with HRM compared with conventional manometry¹¹ because of easier catheter positioning and no need for LES pull-throughs. A recent study indicated that medical students could learn how to interpret manometric data more rapidly and accurately when presented in a spatiotemporal representation (HRM with topography) compared with a linear plot (conventional manometry).¹²

Manometry may be anxiety provoking and uncomfortable for patients because it is usually performed without

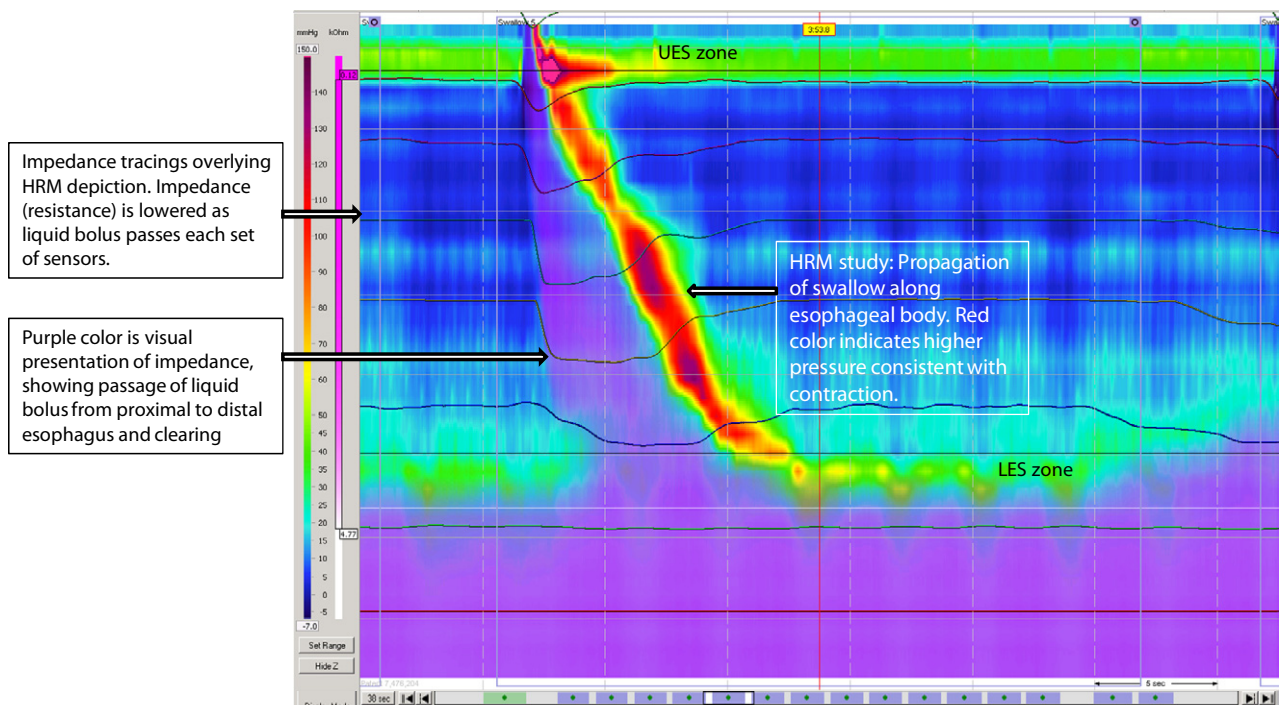


Figure 2. High-resolution manometry and impedance study. This is a single, normal swallow. Color bar along the left side shows that red depicts higher pressure contraction and blue is low pressure. Liquid swallow is propagated normally from proximal (upper esophageal sphincter [UES]) to distal (lower esophageal sphincter [LES]). Impedance line tracings are overlying the color and show that impedance is decreased as the liquid bolus passes each set of sensors on the catheter. Purple visually depicts the impedance and can be thought of as a column of barium: the swallowed water passes through from proximal to distal and clears.

sedation. Patient cooperation is crucial to performing a sound technical study, and a clear explanation of what the patient will experience throughout the procedure should be provided.⁵

Outcomes and comparative data

Outcome and comparative studies have focused on the role of conventional and high-resolution esophageal manometry in the diagnosis and therapeutic management of esophageal disorders.

Several trials suggest that dysmotility found on preoperative conventional manometry does not predict postoperative dysphagia after an antireflux procedure.¹³⁻¹⁵ However, these studies did not include large numbers of patients with severe motility disorders. In clinical practice, esophageal manometry is frequently performed to identify these patients before antireflux surgery.

One study showed that HRM testing may be able to divide achalasia patients into subtypes who are more or less likely to respond to different treatment modalities.¹⁶

A prospective study found that 24-hour ambulatory manometry was more likely to detect diffuse esophageal spasm compared with conventional manometry.¹⁷ However, 24-hour manometry is not commonly performed in clinical practice.

Few studies exist comparing the technical aspects and performance of conventional and those of HRM. In a large

prospective study of 212 patients that compared HRM with simulated conventional manometry (ie, data extrapolated from only 4 HRM sensors), the 2 methods had a high rate of agreement ($\chi^2 = 1.22, P = .88$), but the conventional method failed to identify 6 of 26 patients with achalasia.¹⁸ A small prospective study of 40 patients demonstrated significantly lower procedure times for HRM compared with conventional manometry with impedance (8.1 vs 24.4 minutes; $P < .0001$).¹¹ In another small study of 19 patients, HRM was found to be superior to simulated conventional manometry for predicting successful swallow propagation (90% sensitivity vs 70% specificity; 100% vs 89%, respectively), by using video fluoroscopy as the criterion standard.¹⁹ Another study found that LES resting lengths and pressures were greater with HRM with and without the eSleeve compared with conventional manometry with the pull-through technique.²⁰

Safety

Esophageal manometry is considered a safe test. Patients are informed before the procedure that they may experience mild sore throat, nasal congestion, or epistaxis.²¹ Inadvertent tracheal intubation may occur. These adverse events are usually self-limited. More serious side effects are extremely rare; there is a single report of esophageal perforation.²² There are theoretical concerns about

performing manometry in patients with an unrecognized Zenker's diverticulum.

Another relevant issue in the safety of esophageal manometry includes concerns of the sterility of reusable manometric catheters and water-perfusion systems in which bacterial overgrowth with water-associated organisms could occur. However, there are no published reports of transmission of infection via these routes. Disposable protective sheaths fitting over reusable manometry catheters are available (ManoSheath; Sierra Scientific) but there are no data to suggest an advantage compared with high-level disinfection alone. Manufacturers provide user manuals for reusable equipment that provide instructions on high-level disinfection protocols.

Financial

Pricing of esophageal manometry systems and accessories is found in Tables 1 and 3 through 5. In general, conventional manometry configurations are less expensive than HRM systems. Manufacturers may provide the option of purchasing all-inclusive packages or custom configurations that meet specific needs. Additional accessories may need to be purchased (eg, computer, printer, interface for solid-state or water-perfusion transducers, individual transducers, air pressure cuffs). Some packages include impedance capabilities, which add to the costs.

CPT codes for the procedure are noted in Tables 6 and 7.

Areas of future research

Previous studies on esophageal manometry have been based on normal values and criteria defined by conventional manometry. Inconsistencies in technique among laboratories may challenge these standards and the validity of many outcome/comparative studies. Studies are needed to determine whether HRM data are more reproducible and can provide a more complete understanding of esophageal motility disorders. For example, recent publications on HRM have proposed a new subclassification for achalasia. Further studies are necessary to determine whether these distinctions translate to superior diagnosis or treatment strategies for achalasia and other disorders. Few studies address the utility of HRM for diffuse esophageal spasm, and future research may determine whether this condition is a distinct entity or a possible variant of achalasia or lies within the spectrum of nonspecific motility disorders. Better characterization of this and other nonspecific esophageal conditions through HRM research may aid in identifying effective treatment. Finally, further research is needed to determine whether HRM is superior to conventional manometry for the prediction of dysphagia after reflux surgery.

Summary

Esophageal manometry has been used for decades to evaluate esophageal function and to identify motility disorders. HRM technology may provide a better understand-

ing of esophageal physiology as well as the potential for improvement in diagnosis and treatment of various motility disorders. Further studies are needed to determine the full potential of HRM in clinical practice.

PART II: IMPEDANCE

Background

MII testing is a catheter-based method of assessing bolus movement within the esophagus. It can be combined with pH testing or with manometry, depending on the clinical information needed. When combined with manometry, it provides simultaneous data on bolus transit and contractions to identify whether a functional defect is present.²³ When combined with pH testing, impedance can identify reflux whether the refluxate is acidic and can provide correlation between reflux episodes and symptoms to help guide management.

Technology under review

The principles of impedance were first applied to the GI tract in 1991.²⁴ MII testing was approved by the U.S. Food and Drug Administration for esophageal function testing in 2002. Impedance measures changes in resistance (in ohms) of alternating electrical current passing through pairs of metal rings on a catheter. In the empty esophagus, baseline current is conducted between the rings by ions on the mucosa. Because impedance catheters have multiple sets of impedance-measuring rings, bolus movement and direction (antegrade or retrograde) can be assessed.²⁵ When a liquid bolus passes the metal rings, the impedance (resistance) rapidly decreases because of increased ion conductivity through the liquid, returning to baseline once the bolus has passed. A liquid swallow causes impedance to decrease sequentially from the proximal to distal esophagus, whereas liquid gastroesophageal reflux causes impedance to decrease sequentially in a retrograde manner. Air conducts current poorly (ie, it has a high impedance), so air boluses that are swallowed or belched are detected by a dramatic increase in impedance.

Several impedance-monitoring devices are commercially available for esophageal function testing (Tables 3 and 4). Separate equipment is required for MII plus pH (MII-pH) or MII plus manometry (MII-EM) testing and includes a catheter, a data recorder, a dedicated computer, and proprietary software to interpret the data.

MII-pH catheters are long, flexible tubes made of polyurethane in a variety of diameters and lengths. The catheters have multiple impedance sensor pairs along their length and 1 or 2 pH sensors made of either glass or antimony. The standard MII or MII-pH catheter has 6 to 8 pairs of impedance sensors that collect data 3, 5, 7, 9, 15, and 17 cm proximal to the LES.²⁶ Reusable and single-use catheters are available.

MII-EM catheters are available from 2 manufacturers (Sandhill Scientific and Medical Measurement Systems)

TABLE 3. Esophageal manometry accessories: catheters

Company	Description	Type	Specifications	Cost
Arndorfer Medical Specialties	3X standard esophageal	Water perfusion, conventional	3.6-mm diameter, 3 channels	\$120
	Manometry catheter 4X standard esophageal	Water perfusion, conventional		\$150
	Manometry catheter M ³ 4 lumen with center	Water perfusion, conventional	4.8-mm diameter, 4 channels with central lumen for pH probe	\$225
	M ³ 6 lumen with center	Water perfusion conventional	4.8-mm diameter, 6 channels with central lumen for pH probe	\$270
	M ³ 6 lumen radial with center	Water perfusion, conventional	4.8-mm diameter, 6 channels with central lumen for pH probe; 3 channels lie in same openings of distal catheter	\$270
	M ³ 8 Standard	Water perfusion, conventional	4.8-mm diameter, 8 channels	\$325
	M ³ 8 lumen radial with center	Water perfusion, conventional	4.8-mm diameter, 8 channels with central lumen for pH probe; 4 openings lie in same position of distal catheter	\$325
	M ³ interfaced with AMS sleeve	Water perfusion, conventional	4.8-mm diameter with sleeve attachment	\$775
	Custom catheter	Water perfusion, conventional	4.8-mm diameter, variable number of channels with central lumen for pH probe	TBD
	Dentsleeve	Side-hole catheters, various models	Water-perfusion catheters	2.5-4.7 mm diameter, 4-21 channels
Sleeve sensor catheters, various models		Water-perfusion catheters	2.5-4.7 mm diameter, 7-21 channels, with or without stiffener	Contact company
Latitude	Esophageal manometry probe GIM-6000E	Air-charged conventional	2.7-mm diameter, 4-channel circumferential sensors; disposable, package of 5	\$300
Medical Measurement Systems*	MMS G-84300	Water perfusion, conventional	9F diameter; 4 channels with central lumen; disposable, box of 20	\$680
	MMS G-84301	Water perfusion, conventional	9F (3-mm) diameter, 4 channels with central lumen; disposable, box of 20	\$680
	MMS G-88402	Water perfusion, conventional	12F (4-mm) diameter, 8 channels with central lumen; disposable, box of 20	\$1040
	MMS G-90030	Water perfusion, conventional	3.9-mm diameter, 8 channels; disposable, box of 10	\$560
	MMS G-90060	Water perfusion, conventional	3.2-mm diameter, 4 channels; disposable, box of 10	\$340
	MMS G-90500	Water perfusion, high resolution	4.42-mm diameter, 20 channels; disposable, box of 10	\$890
Mui Scientific	SE 8-0-0-0-5-5-5-5	Water perfusion, conventional	12F (4-mm) diameter, 8 channels; disposable; 4 openings lie in same position at distal catheter	Contact company
Sandhill Scientific	HRIM catheter	Solid state, high resolution/impedance	12F (4-mm) or 8F (2.7-mm) diameter, 36 channels: 32 pressure/16 impedance channels	\$14,500
	Water-perfused probes	Water perfusion		\$350

TABLE 3. (continued)

Company	Description	Type	Specifications	Cost
Sierra Scientific	ManoScan esophageal catheter	Solid state, high resolution	4.2-mm diameter, 36 pressure channels (circumferential)	\$9900
	ManoScan Z catheter	Solid state, high resolution/impedance	4.2-mm diameter, 36 pressure channels (circumferential)/18 impedance channels	\$12,000
	ManoScan esophageal 3D catheter	Solid state, high resolution	4.2-mm diameter, 32 HRM (circumferential)/12 high definition	\$13,500
	Small-body catheter	Solid state, high resolution	8F (2.7-mm) diameter, 12 channels	\$10,900
	Adult small-diameter catheter	Solid state, high resolution	8F (2.7-mm) diameter, 12 channels	\$10,900

TBD, To be determined; HRIM, high-resolution impedance manometry; 3D, 3-dimensional; HRM, high-resolution manometry.

*Additionally offer reusable water-perfused and solid-state HRM/impedance catheters.

TABLE 4. Esophageal manometry accessories: water perfusion pumps

Company	Description	Power source	Cost
Arndorfer Medical Specialties	4-channel hydraulic capillary infusion system,	Nitrogen	\$3595
	8-channel hydraulic capillary infusion System	Nitrogen	\$4195
	12-channel hydraulic capillary infusion system	Nitrogen	\$5895
Dentsleeve	8-channel Mark II horizontal deck pump	Electric	Contact company
	8-channel Mark III vertical trolley mounted pump	Electric	Contact company
Medical Measurement Systems	Solar manometric perfusion pump (various pressure channels)	Electric	\$5000-7000
Mui Scientific	Electric perfusion pump (4, 6, 8, or 12 channel)	Electric	Contact company
	Nitrogen perfusion pump (4, 6, 8, or 12 channel)	Nitrogen	Contact company

and are available with HRM. These are also made of flexible polyurethane, which softens in response to heat to ease patient comfort. The HRM impedance catheters range in diameter from 8F to 12F and have 12 to 18 pairs of impedance-measuring rings and 32 to 36 pressure sensors. There are impedance rings on either side of each pressure sensor except the most distal one so that impedance data can be correlated with manometry data in a given area.

The data recorder is integrated with each manufacturer's catheter. Catheters are compatible only with data recorders from the same company. The data are stored on a memory card and then downloaded to a dedicated workstation.

The proprietary software is an essential component of the technology. Although manual interpretation of the raw data can be performed, the software is designed to provide an automated analysis of the data. This automated analysis may facilitate but should not replace interpretation by a clinician. The software identifies individual reflux and swallow events, performs symptom-associated analysis, and distinguishes changes in impedance that are not clin-

ically important to improve efficiency of reading.²⁷ There are built-in tools to allow for more detailed interpretation of the data. A customized report is generated to document the interpretation, some with color graphics and images (Fig. 2).

Each of the manufacturers provides training in use of the MII system.

Technique

Before MII-pH or MII-EM testing, patients are asked to fast overnight. They may take their usual medications before the procedure. Before MII-pH testing, it should be clarified whether MII-pH testing is to be performed with the patient on or off a proton pump inhibitor (PPI) therapy. In patients with refractory GERD symptoms, MII-pH testing is intended to detect nonacid reflux as a cause of ongoing symptoms. Therefore, PPI therapy is usually continued for the examination.

For MII-pH studies, the pH sensor must be calibrated with buffer solutions before insertion in accordance with manufacturer instructions. The catheter is then placed

TABLE 5. Esophageal function testing (manometry and impedance): hospital outpatient reimbursement codes, national Medicare coverage, and payment

CPT	Description	Physician payment	Hospital payment
91010	Esophageal motility (manometric study of the esophagus and/or gastroesophageal junction) study	\$62.53	\$239.03
91037	Esophageal function test, gastroesophageal reflux test with nasal catheter intraluminal impedance electrode(s) placement, recording, analysis, and interpretation	\$48.89	\$239.03

CPT, Current Procedural Terminology.

TABLE 6. Esophageal function testing (manometry and impedance): physician office, national Medicare coverage, and payment*

CPT	Description	Nonfacility (global) payment
91010	Esophageal motility (manometric study of the esophagus and/or gastroesophageal junction) study	\$206.92
91037	Esophageal function test, gastroesophageal reflux test with nasal catheter intraluminal impedance electrode(s) placement, recording, analysis, and interpretation	\$152.73

CPT, Current Procedural Terminology.

*No coverage in ambulatory surgery center setting for any of these procedures.

transnasally such that the proximal pH sensor is 5 cm above the LES, and the distal pH sensor, if present, is 10 cm below the LES in the stomach. These landmarks are typically determined by previous manometry, endoscopy, or an LES locator balloon on the catheter. The proximal end of the catheter emerging from the patient's nose is affixed to the face with tape for the duration of the test. The catheter is connected to a recording system that is low profile and is worn by the patient. The patient is urged to continue all routine daily activities and diet, including those activities known to precipitate symptoms because changes in typical routines may affect data interpretation. During the study, events (meals, supine, upright positions) and symptoms are entered into the recording apparatus and/or a diary. Recorded events and symptoms later can be correlated with the downloaded data, similar to stan-

dard pH testing. Once the study is completed, the recording unit is returned to the clinician, and the study is downloaded to the computer. MII-pH tests typically last 24 hours.

For MII-EM studies, the catheter is also placed transnasally, typically in an unседated patient. Topical nasal sedation is commonly used. After initial passage of the distal 10 to 15 cm of the HRM catheter into the stomach (where the ports are zeroed to gastric baseline pressures), the catheter is pulled back until distal ports are positioned within the high-pressure zone of the LES, as determined manometrically. The precise location of pressure and impedance sensors depends on the configuration of the catheter used. For example, with an HRM catheter with 32 pressure sensors and 4 impedance sensors, the distal 3 to 5 pressure sensors remain within the stomach, 3 to 5 pressure sensors straddle the LES, and 22 to 26 sensors are located within the esophageal body, UES, and pharynx. The impedance sensors are located at 5, 10, 15, and 20 cm proximal to the LES. After placement, the supine patient is asked to take 10 liquid (normal saline solution) and 10 viscous (proprietary viscous solution, Sandhill Scientific) swallows of 5 mL each, 20 to 30 seconds apart. Normal saline solution is used because it has a standard ionic concentration (unlike water) and provides more predictable impedance changes. MII-EM testing takes approximately 20 to 30 minutes.

After completion of either type of study, the data are analyzed by the proprietary software and interpreted by the reporting physician. Standardized interpretation of pH data and manometry data is based on published literature.^{28,29} Normal values for both MII-pH and MII-EM testing have been derived from studies of healthy volunteers.

During MII-EM testing, the impedance-detected swallows are considered complete if bolus entry occurs at the most proximal sensor and passes completely through the remaining sensors including the most distal one at 5 cm above the LES. The impedance portion of the study is considered abnormal if more than 30% of liquid swallows show incomplete bolus transit or more than 40% of viscous swallows show incomplete bolus transit.³⁰

For MII-pH testing, normal values differ depending on whether the patient is on or off PPI therapy. The parameters measured for an MII-pH study include the number of reflux events, type of refluxate, refluxate presence time, and refluxate clearance time (the total amount of time that the refluxate is present at 5 cm above the LES and the average duration of time that liquid is present during a reflux episode, respectively). Normal values for MII-pH tests were derived from studies of healthy volunteers³¹⁻³³ and are listed in Table 5.

A symptom index or symptom-associated probability (SAP) reading is also generated to help correlate symptoms with reflux episodes. The symptom index is defined as the number of reflux events associated with symptoms divided by the total number of reflux episodes. A symptom

TABLE 7. Normal values for combined MII-pH monitoring

	U.S.-Belgian (n = 60) ³¹	French-Belgian (n = 72) ³²	Italian (n = 25) ³³
Esophageal pH data, % time pH <4			
Total, %	6.7	5.0	4.0
Upright, %	9.7	6.2	5.0
Recumbent, %	2.1	5.3	3.0
Esophageal MII data, no. of reflux episodes			
Total	73	75	61
Acid	55	50	51
Weakly acid	26	33	38
Weakly alkaline	1	15	18

MII-pH, Multichannel intraluminal impedance plus pH.

index of greater than 50 (eg, more than half of the total number of reflux events were symptomatic) is considered a positive test. SAP is another method of calculating whether symptoms are associated with reflux and is sometimes used instead of the symptom index.

Indications and efficacy

MII-pH testing. MII-pH testing is usually performed for evaluation of reflux symptoms, particularly in patients with incomplete or no response to PPI therapy.³⁴ In this clinical situation, impedance testing is intended to assess whether nonacid reflux is the cause of ongoing symptoms. A reflux event can be detected whether it is acidic (pH <4.0) or not, and these data can be correlated with the patient's symptoms to guide clinical decision making.³⁵ Nonacid reflux can be further characterized as weakly acidic (pH 4-7) or weakly alkaline (pH >7),³⁶ although the clinical utility of this distinction has not been defined. Additionally, the proximal extent of reflux can be assessed, the type of refluxate can be determined (gas, mixed, or liquid), and a calculated symptom index can help assess whether the ongoing symptoms are correlated with reflux events. Because the test is usually being done to assess whether nonacid reflux is the cause of persistent symptoms, MII-pH testing is usually done when the patient is on acid suppression therapy. Limitations of MII-pH testing include the inability to assess the volume of refluxate as well as difficulty in measuring impedance changes in certain populations that have a low baseline impedance (eg, Barrett's esophagus, severe esophagitis, ineffective esophageal motility).³⁷

A number of studies have evaluated the utility of impedance testing in GERD patients both on and off PPI therapy.³⁸⁻⁴³ A study of 60 patients showed a higher SAP with MII-pH testing compared with pH testing alone off

PPI therapy (77.1% vs 66.7%, $P < .05$).³⁸ A study of 150 patients with nonerosive reflux disease who had undergone MII-pH testing off PPI therapy found that 87 patients (58%) had a normal esophageal acid exposure. However, 15% of these had a positive SAP for acid, 12% for nonacid, and 5% for both.³⁹ Two studies aimed to clarify what makes reflux events symptomatic and found that a higher proximal extent, greater pH decrease, prolonged acid clearance time, and mixed composition reflux (air and liquid) were more likely to be associated with symptoms.^{40,41} These studies suggest that MII-pH testing off PPI in patients with typical symptoms may be slightly more sensitive than pH testing alone, but the incremental benefit is small.

Combined MII-pH monitoring was done in 168 patients with persistent GERD symptoms despite twice-daily PPI therapy. The majority of patients (86%) were symptomatic during the test, but more than half of the symptomatic patients had a negative symptom index (eg, symptoms did not correlate with a reflux event). Of the 69 patients with a positive symptom index, acid reflux was the cause in 11% and nonacid reflux in 37%, which was only detectable by impedance.⁴² A multicenter study of 150 patients showed that a positive SAP was found in association with nonacid reflux in 32%.⁴³ These studies suggest that 30% to 40% of patients with persistent symptoms on PPI therapy have nonacid reflux as a cause, and this can currently only be identified with impedance testing.

GERD as a cause of atypical reflux symptoms (eg, cough, hoarseness) may be identified with MII-pH testing. In a study of 22 patients with unexplained chronic cough who underwent MII-pH testing, 30.6% of coughing episodes were associated with reflux.⁴⁴ A second study of MII-pH in 100 patients with unexplained chronic cough

found that chronic cough was temporally associated with a reflux event in almost 50% of patients.⁴⁵ A third study of 50 patients with cough on PPI therapy found that nonacid reflux events were associated with cough in 26%; 6 of these patients had antireflux surgery and responded favorably.⁴⁶ Finally, a study of 37 patients with chronic cough (n = 18) and asthma (n = 19) showed a positive SAP in 7 of 26 patients.⁴⁷ Compared with SAP-negative patients, those who were SAP positive had more reflux episodes and more events that reached the pharynx, suggesting that more proximal reflux episodes detectable by impedance have a greater likelihood of producing chronic cough. In summary, these studies suggest that MII-pH testing may diagnose GERD as a cause of chronic cough in some patients that would be missed with only pH testing.

There are limited data on the utility of MII-pH testing to select patients for Nissen fundoplication, with mixed results. A small retrospective study of 19 patients who had MII-pH testing before Nissen fundoplication found that 94% of patients who had a positive symptom index before surgery were asymptomatic with regard to GERD after surgery, and 2 with a negative preoperative symptom index had recurrent symptoms.⁴⁸ Another study of 153 patients found no differences in postoperative symptom recurrence or dysphagia based on whether findings on preoperative MII-pH testing were normal or abnormal.⁴⁹ A retrospective study of 62 post-Nissen fundoplication patients who underwent esophageal manometry and MII-pH testing and completed symptom questionnaires at 6 months postoperatively also found that findings on impedance testing postoperatively were not predictive of symptom improvement.⁵⁰ These few studies suggest that MII testing is of limited utility in the assessment of patients before and after antireflux surgery, although large controlled trials are lacking.

MII-EM testing. MII-EM testing may be useful to evaluate dysphagia, odynophagia, chest pain, and regurgitation after exclusion of esophageal structural abnormalities. Standard manometry does not demonstrate whether a contraction results in actual bolus passage. In contrast, MII-EM testing can assess both contraction and bolus clearance. Impedance testing has been compared with video fluoroscopy in studies of normal volunteers,^{51,52} in whom changes in impedance correlated with radiographic bolus movement in 97% (72/74) of swallows.⁵³

Several studies assessed impedance findings in patients with normal and abnormal manometry testing results. A multicenter study of 43 healthy volunteers showed that 97% of manometrically normal liquid swallows had complete bolus transit by impedance, but that nearly half of manometrically ineffective liquid swallows also had normal bolus transit.⁵³ In a large prospective study, 350 patients referred for a variety of esophageal symptoms (primarily dysphagia, heartburn, and chest pain) underwent manometry and impedance testing.⁵⁴ No patient with achalasia or scleroderma had normal bolus transit. Of

patients with manometric diagnoses of ineffective esophageal motility or diffuse esophageal spasm, 51% to 55% had normal bolus transit on impedance. More than 95% of those with nutcracker esophagus (elevated LES pressure) or other isolated LES abnormalities (eg, poorly relaxing LES, hyper- or hypotensive LES) had normal transit, suggesting that esophageal body pressures are the primary determinant of bolus transit. Another study aimed to clarify the value of adding impedance testing to manometry in patients with dysphagia without obstruction in 40 consecutive patients.⁵⁵ Abnormal bolus transit was found in 35.3% of patients with normal manometry, in 66.7% of those with diffuse esophageal spasm, and in 100% of achalasia patients. Multiple other studies of patients with a manometric diagnosis of ineffective esophageal motility or diffuse esophageal spasm showed that bolus transit is abnormal in approximately 50%.^{56,57} Abnormal bolus transit on impedance testing correlated well with dysphagia symptomatology. Other studies showed that impedance testing is difficult to perform in patients with achalasia caused by low baseline impedance, fluid regurgitation, and air trapping.^{58,59} In summary, these studies suggest that impedance monitoring is probably not a useful addition in patients with severe motor abnormalities such as achalasia, but may identify a functional defect in approximately half of patients with ineffective esophageal motility or diffuse esophageal spasm.

Other studies have sought to clarify the clinical utility of impedance testing in patients with normal manometry. Of 576 consecutive patients who underwent MII-manometry testing for a variety of symptoms, 158 were found to have normal manometry and abnormal impedance.⁶⁰ Abnormal bolus transit for viscous, liquid, and both types of swallow was found in 60%, 19%, and 21%, respectively. The patients with abnormal impedance were more likely to have presented with dysphagia (23% vs 10%, $P = .0035$). Taken together, these studies suggest that in patients with non-obstructive dysphagia and normal manometry, impedance testing will identify a subset of patients with impaired bolus transit.

MII-EM has been used to evaluate dysphagia in fundoplication patients both pre- and postoperatively in 2 studies. A prospective study evaluated 74 patients with preoperative symptom questionnaires, 24-hour pH testing, and MII-EM, and all completed symptom questionnaires at 18 months postoperatively.⁶¹ There were no differences in preoperative MII-EM and pH study findings in those with preoperative dysphagia compared with those without, and abnormal preoperative bolus transit on MII-EM did not predict postoperative dysphagia. The only factor that correlated with postoperative dysphagia was preoperative dysphagia. MII-EM testing has also been used to assess patients with postfundoplication dysphagia. A study of 80 consecutive postfundoplication patients found that those with dysphagia were more likely to have impaired bolus clearance on MII testing (62% vs 32%, $P = .01$), although

manometric findings of impaired peristalsis were similar (17% vs 14%).⁶²

Finally, MII-EM has been used to evaluate patients with chronic belching, suspected rumination syndrome, and suspected aerophagia. In these populations, abnormal air swallowing and expulsion patterns were demonstrated by using impedance.⁶³⁻⁶⁶

Comparative data

Several studies have been conducted to evaluate interobserver agreement in MII-pH testing. Good interobserver agreement has been demonstrated in the pediatric population.⁶⁷ Another study described moderate interobserver agreement between multiple reviewers versus automated software interpretation (Autoscan; Sandhill Scientific), although this may be on the basis of experience because 2 of the reviewers interpreted more than 90% of the studies.⁶⁸ Two studies demonstrated the reproducibility between Autoscan and individual analysis of impedance/pH data.^{69,70}

Ease of use

Placement of a transnasal catheter may produce nasopharyngeal discomfort, although this rarely necessitates termination of the procedure. The presence of the catheter may hamper usual activities and food and drink consumption. Despite these limitations, most patients are able to complete the entire 24-hour examination.

Each study must be reviewed by an experienced operator. Without the use of automated software, the interpretation is time-consuming and laborious.

Safety

There have been no reported complications caused by impedance monitoring. The contraindications for placement of transnasal instruments may include previous nasal surgery or trauma, coagulopathy, and the concurrent use of anticoagulants.⁷¹ The voltage generated by the transducer is limited to 8 μ A of current, which is well below the threshold for cardiac stimulation.⁷² Safety data on the use of impedance in patients with implantable cardiac defibrillators and pacemakers have not been reported, however.

Financial considerations

The cost of impedance depends on the capital cost of the equipment plus the use of the disposable catheters. Current pricing information for the various components of impedance testing is provided in Tables 3 and 4.

The CPT (Current Procedural Terminology) code for esophageal function testing (including catheter pH testing and impedance testing) is 91037 (Table 7).

Areas for future research

Studies have detailed the impedance findings in patients before and after antireflux surgery, refractory GERD, atypical symptoms of GERD, and nonspecific motility dis-

orders. The next step should be the performance of outcomes studies in these settings to see whether impedance has an overall impact on clinical course. Formal cost analyses evaluating whether impedance is a cost-effective tool in the management of patients with refractory GERD and nonobstructive dysphagia have not been performed. Comparative studies of MII impedance and HRM should be performed to determine the utility of the addition of impedance in GERD patients.

Summary

Impedance testing provides additional clinical information compared with pH testing alone in the diagnosis of patients with reflux symptoms, especially when atypical symptoms are present or the response to PPI has been inadequate. It may be helpful to the clinician to categorize patients with symptoms truly attributable to reflux versus another cause of symptoms (eg, functional heartburn), although outcomes studies have not been performed to determine whether this truly leads to a change in management. MII-EM testing can diagnose whether a functional defect truly exists in patients with dysphagia and other symptoms such as noncardiac chest pain, especially in patients with manometric diagnoses of ineffective esophageal motility and diffuse esophageal spasm. Improved outcomes based on MII-EM testing may be difficult to demonstrate because of the lack of effective therapy for these patients. The results of future studies should clarify when impedance testing should be performed and what change in management can be expected based on the results, as well as the relative cost benefit of such testing.

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Abbreviations: HRM, high-resolution manometry; LES, lower esophageal sphincter; MII, multichannel intraluminal impedance; MII-EM, multichannel intraluminal impedance plus manometry; MII-pH, multichannel intraluminal impedance plus pH; PPI, proton pump inhibitor; SAP, symptom-associated probability; UES, upper esophageal sphincter.

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