

PREFACE

Ascona 2011: Proceedings of the HRM Working Group Conference—Introduction for the Proceedings of the Ascona Conference on Advances in Clinical Investigation of Esophageal Dysmotility and Reflux Disease

In April 2011, a conference ‘Advances in clinical investigation of esophageal dysmotility and reflux disease’ was held in Ascona, Switzerland. The conference was organized by members of the High-Resolution Manometry Working Group chaired by Associate Professor Dr. Mark Fox to bring together an international group of physicians and scientists with the aim to:

- 1 Introduce the new ‘Chicago Classification Criteria of Esophageal Motility Disorders Defined in High Resolution Esophageal Pressure Topography’.
- 2 To present guidelines that incorporate the current state of the art for investigation and management of esophageal motility disorders and gastro-esophageal reflux disease.
- 3 To provide practical training to ensure best practice and maximum patient benefit wherever these technologies are applied.

The Ascona meeting was supported by all the leading manufacturers of diagnostic instruments utilized in the assessment of esophageal motility and gastro-esophageal reflux. Industry representatives and engineers attended as observers because the clinical practice of esophagology is inseparable from developments in hardware and software.

The key outcome of the Ascona meeting was the introduction of the ‘Chicago Classification of esophageal motility disorders’, the culmination of a series of meetings of the High-Resolution Manometry Working

Group that began in San Diego at Digestive Disease Week 2008. The core content of the classification scheme was approved by the Working Group in Ascona and the lead authors were then charged with drafting the manuscript for publication in this supplement of *Neurogastroenterology and Motility*. This classification scheme is built on robust experimental data, and provides a clinically relevant hierarchy of diagnosis. It has been endorsed by both the European and American Neurogastroenterology and Motility Societies in addition to many other professional organizations. The authors hope that this unique consensus will not only promote better understanding of esophageal motility disorders amongst clinicians, but also provide a solid foundation for future research. Additionally this supplement provides a collection of focused topic reviews, highlights of the Ascona conference, on specific aspects of esophagology that reference the Chicago Classification and its use in clinical practice.

Thus, on behalf of the members of the High-resolution Manometry Working Group, the Editorial Board of *Neurogastroenterology and Motility* and finally the professional organizations who have provided their endorsement of the Chicago Classification, we present the proceedings of the Ascona Conference.

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REVIEW ARTICLE

High resolution manometry: the Ray Clouse legacy

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Esophageal manometry assesses pressure phenomena, peristalsis and bolus transit in the esophagus. Older 'conventional' manometry techniques recorded esophageal peristalsis using 5–8 widely spaced water perfused channels in an esophageal motility catheter. Two significant advances in the 1990s, an increase in pressure sensors along the catheter, and use of spatiotemporal plots for data display, led to what is now recognized as high-resolution manometry (HRM).^{1,2} HRM was the concept and innovation of a remarkable esophagologist, researcher and educator, the late Ray Eugene Clouse, MD.

HRM has its roots in conventional perfused manometry. Clouse decided that the esophagus was holding secrets between the widely spaced recording points of his conventional manometry catheter. He tested his hypothesis by continuing the pull through maneuver 1 cm at a time till the last recording channels reached the upper esophageal sphincter (UES), obtaining at least one wet swallow at each station.¹ When the swallows were aligned, the jumble of tracings he obtained could not be easily interpreted. It was time for another Clouse innovation – the spatiotemporal contour plot. Clouse, along with Annamaria Staiano, MD, digitized the tracings using a hand held digitizer, and assigned colors to amplitude levels.^{1,2} Software programs provided best fit data points in between the recording sites. The final result was a smooth topographic map of the esophageal peristaltic wave. Since amplitudes were color coded, topographic contours could be viewed

from above as a spatiotemporal plot (Fig. 1). We now recognize these plots as a characteristic of HRM.

Next, Clouse worked on streamlining the process of data acquisition. Collaboration with Dentsleeve resulted in a 0.4 cm extruded, 21 lumen silicon water perfused catheter, and complementary software was developed by Medical Measurement Systems (MMS, Enschede, Holland).^{2,3} The manometry procedure remained cumbersome, the pull through maneuver had not been eliminated, and only 75–80% of the esophagus could be interrogated at a time. Nevertheless, there were significant advances in our understanding of esophageal peristalsis, which was now shown to consist of a chain of contracting segments

Table 1 Original concepts of HRM utilization

Evaluation	Applicability
Pharyngo-UES function	
Nature of motor disorder	Clinical/research
Peristaltic integrity	
Contraction segments, segmental abnormalities	Research/clinical
Types of severe dysfunction	Clinical/research
New motor patterns	Clinical/research
LES dysfunction	
Achalasia	Clinical/research
Incomplete obstructive patterns	Research/clinical
Fundoplication errors	Clinical/research
Anatomic considerations	
Location of LES	Clinical
Esophageal length	Clinical
Hiatus hernia	Clinical/research
Motility education	Education/clinical/research
Future direction	
3D HRM	Research
HRIM	Research/clinical
Outcome studies	Research

UES, upper esophageal sphincter; LES, lower esophageal sphincter; HRIM, high resolution impedance manometry.

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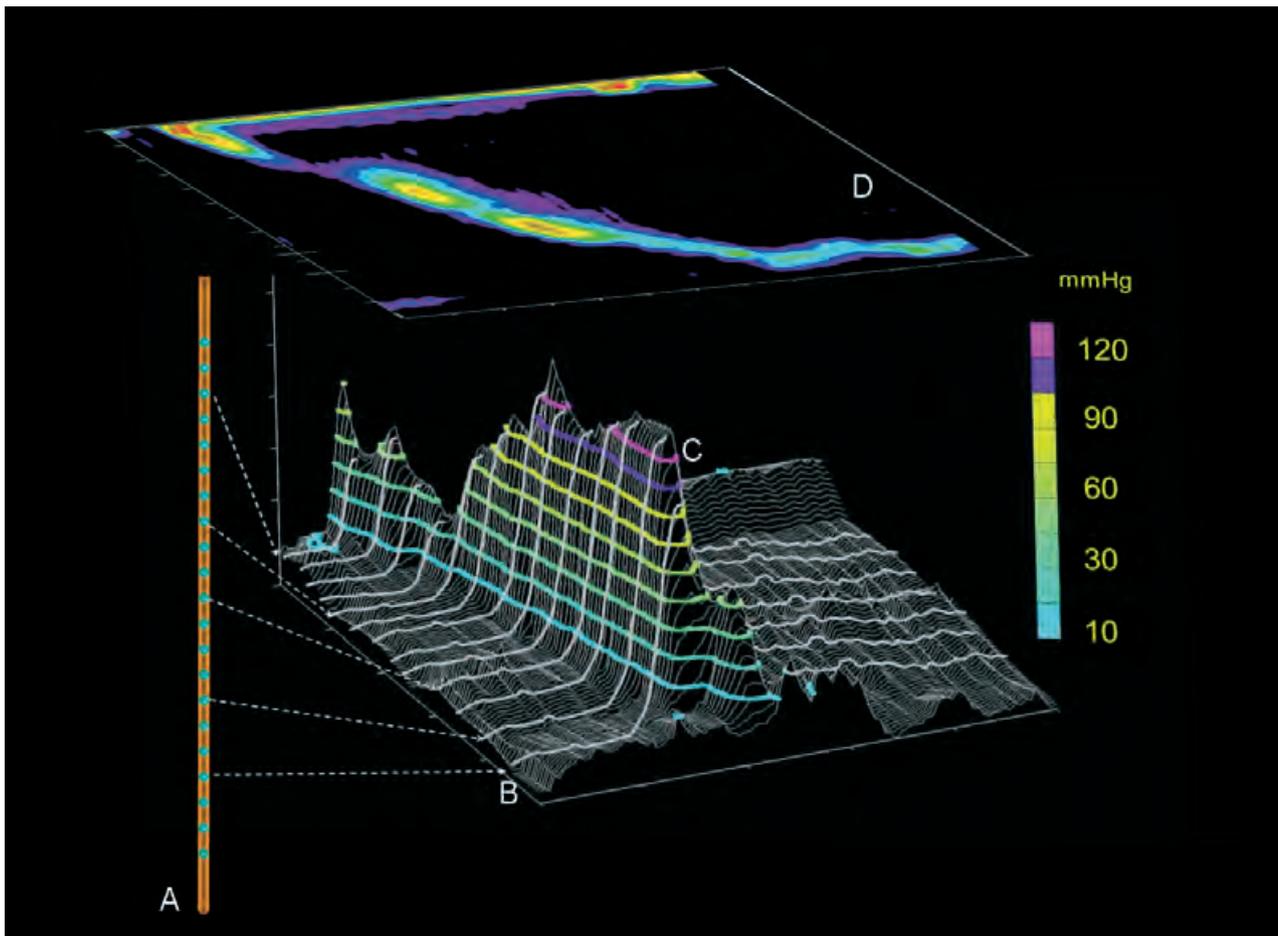


Figure 1 The concept of high resolution manometry (HRM). Closely spaced recording sensors on an esophageal motility catheter (A) generate multiple recordings throughout the esophagus (B). Dashed arrows point to pressure recordings from individual sensors. Computer software fills in best fit data between the recording sensors 1 cm apart, and color codes amplitude levels (C). Finally, the image is smoothed out electronically, and displayed as a topographic contour plot (D) representing the peristaltic sequence when viewed from above. The contour plots are termed Clouse plots in honor of Ray Clouse, who developed HRM.

separated by troughs.⁴ We quickly learned that esophageal smooth muscle consisted of not one but two contracting segments.⁵ These segments merged together in hypercontractile states, and demonstrated wide troughs and low amplitudes in hypomotility disorders.⁴⁻⁶ We also learned that esophageal shortening could move the lower esophageal sphincter (LES) proximal to even sleeve LES sensors, and that HRM provided higher accuracy in achalasia diagnosis because LES excursion could be followed and abnormal relaxation documented despite this shortening.^{7,8} Many motor disorders were associated with recognizable HRM patterns, and diagnoses could be made with just pattern recognition in many instances. But the system was not yet optimal for widespread clinical use, and more work is needed to be done.

As technology progressed toward solid state pressure sensors, Clouse found a key collaborator in Thomas

Parks, PhD, who formed a new company, Sierra Scientific, Inc. to advance the field. The new millennium heralded a collaborative effort which culminated in the development of a solid state catheter, with 36 high fidelity circumferential sensors.⁹ The stationary pull through maneuver was now obsolete, as the entire esophagus from pharynx to stomach could be viewed real time. New software programs were written, and an electronic sleeve was developed to interrogate LES post swallow residual pressures (ManoView™, eSleeve™, Sierra Scientific, Inc., Los Angeles, CA, USA).^{9,10} These baby steps in the early 2000s have been augmented exponentially in the past 5 years, as HRM technology moved from St. Louis to Chicago and beyond.^{11,12} HRM systems are now available from a handful of companies, for not just esophageal manometry (sometimes combined with stationary impedance), but also anorectal, colonic and antroduodenal manom-

etry. An even higher definition technique (3D HRM) uses tactile sensors, and has been introduced for anorectal manometry; it is being researched for detailed interrogation of esophageal sphincters.^{13,14} The following articles only begin to describe the potential this new technology has uncovered in the evaluation of gut motility.

Ray Clouse was a remarkable innovator, with the ability to conceptualize in an abstract and geometric fashion, traits that almost took him to a career in architecture.¹⁵ He developed HRM to simplify esophageal manometry, improve its clinical utility, and to

develop uniformity in data collection and analysis. He envisioned that HRM would make a major impact on clinical and research fronts within esophagology (Table 1), but passed away from terminal cancer before he could fully appreciate the impact of his innovation. The direction HRM has taken in recent years, especially the new clinical classification scheme debuted in this supplement,¹⁶ fulfills many of Clouse's original intent, and would have pleased him immensely. It is only fitting that the HRM plots are now universally termed 'Clouse plots' in his honor. This is the Ray Clouse legacy.

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REVIEW ARTICLE

Technical aspects of clinical high-resolution manometry studies

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Abstract

Background A number of commercial and research systems are available for making high-resolution manometry recordings.

Purpose In this document, we review the standard equipment, patient preparation and routine protocol for high-resolution manometry. The major differences between HRM systems lie in the method of signal transduction, with solid-state catheter systems recording from intraluminal transducers and water perfusion systems recording pressures from external transducers via a perfused silicone catheter. The variations in recording systems result in different mechanical and electrical characteristics which dictate different techniques for setting up and using equipment. These issues are relevant in terms of costs and day to day management, but have little clinical significance. After the equipment is prepared for a manometric study, the esophagus is intubated transnasally with the manometric catheter and the catheter is positioned so that the UES and LES/diaphragm are visualized on the recording screen. The subject then undergoes 10 5ml water swallows in the supine position. Manometric data may be integrated with other data streams such as multichannel impedance or

images from fluoroscopy to increase the power of the technique in difficult cases.

Keywords catheter, high-resolution esophageal manometry, perfusion pump, pressure transducers, solid state.

Abbreviations: HRIM, high-resolution impedance manometry; HRM, high-resolution manometry; LES, lower esophageal sphincter; PIP, pressure inversion point; UES, upper esophageal sphincter.

INTRODUCTION

In this review, we discuss the technical requirements for making high-quality measurements of esophageal pressure and the standard protocol for performing high-resolution manometry (HRM) in routine clinical practice. Analysis of measurements performed using HRM are discussed elsewhere in this supplement.

HARDWARE

The HRM systems consist of a manometric catheter which either contains or is connected to a series of pressure transducers, which are in turn interfaced to signal conditioning circuitry, digitization, display, and recording devices. Complete systems are available commercially from Sierra Scientific Instruments (Los Angeles, CA, USA), Sandhill Scientific (Highlands Ranch, CO, USA) and Medical Measurement Systems (Enschede, The Netherlands).

Pressures in the esophagus are converted to an electrical signal by the pressure transducer. This

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signal, which is initially of low voltage, is amplified and filtered, then digitized using standard circuitry interfaced to a personal computer. The digitized signal is displayed on the computer screen during the study to enable accurate positioning of the manometric catheter and allow technical problems to be resolved at the time of the recording. In parallel, the signal is recorded to a storage device, allowing offline analysis and report generation. Purpose-written software is used to display, edit and analyze the measurements, with data usually presented as a spatiotemporal Esophageal Pressure Topography plot (pressure plotted against both time and distance along the esophagus), a display method which has been shown to improve accuracy and speed of recognition of this form of data.¹

Two main types of manometric catheter are used in HRM studies, solid state and water perfused. The physical and performance characteristics of the systems differ substantially with each having specific advantages and disadvantages (Table 1).

In solid-state manometry, pressure transducers are mounted within the manometric catheter and are therefore at the point of measurement, with consequent benefits for dynamic response. Solid-state catheters are relatively simple to set up and use, but are more vulnerable to damage, the catheters tend to be less comfortable and more expensive, with a shorter lifespan than water-perfused catheters. The electrical characteristics of the transducer vary with temperature, and temperature compensation may therefore be required to normalize the pressures. For some solid-state systems, disposable sheaths are available to reduce the complexity of disinfection. Otherwise, catheters must be disinfected according to local protocol and the manufacturer's instructions; however, solid-state catheters cannot be autoclaved to achieve sterilization. Reproducibility of solid-state HRM has been studied and found to be acceptable.²

In water-perfused manometry, an extruded silicone catheter containing multiple individual channels is perfused with distilled water driven by a pneumatic perfusion pump. Each channel opens to the lumen at a different point on the catheter, and pressures from that point are transmitted back along the column of water to an external transducer in the perfusion pump. These catheters are therefore cheaper, more flexible and thinner than most solid-state catheters, but are more time consuming to set up and technically demanding to use correctly. In addition, the dynamic performance of water-perfused systems is several orders of magnitude less than that of solid-state systems, which is of relevance where rapidly changing pressures must be measured (e.g., in the pharynx/upper esophageal

sphincter (UES) and is dependent on the precise physical arrangement of the system and technique (e.g., perfusion rate, presence of bubbles), as well as varying with pressure. This can be measured as the 'rise rate' (rate at which the pressure rises when the sidehole is occluded). Rise rates of 400 mmHg, which may be difficult to achieve, are required for accurate recording of high pressure contractions and rapidly changing pressures. In contrast, the rise rates of solid-state catheters are in the region of thousands of mmHg/s, although most recording systems do not digitize and record data at a rate that makes use of these characteristics. Pressures recorded using water-perfused catheters must also be adjusted for hydrostatic pressures as well as the offset pressure required to perfuse the water through the catheter itself. Correct use of water perfusion manometry therefore requires more technical skill and training than solid-state manometry, and is subject to more technical problems and limitations. Sterilization can be achieved by autoclaving of silicone water-perfused manometric catheters. As silicone water-perfused catheters have a smaller diameter and are more flexible, in pediatric practice, water-perfused systems are used most often. However, solid-state pediatric catheters with a diameter of 2.75 mm are also available.

A variety of sensor orientations are available in HRM catheters, depending on the technology used. Water-perfused catheters have a unidirectional sensor orientation (measuring pressure at the point of the sidehole), whereas solid-state sensors may be either unidirectional or circumferential, with the circumferential sensors returning a mean pressure rather than pressures in individual directions. Although some of the structures from which pressures are measured do have a radial asymmetry (the UES and LES), the physiological and clinical significance of circumferential vs unidirectional pressure measurement has not been determined, but it seems reasonable that a circumferential system may record more reproducible data from radially asymmetrical structures such as the esophageal sphincters, whereas in the esophageal body, this issue is probably less relevant.²

To measure pressures continuously from the pharynx to the stomach without missing mechanically relevant data, the recording sites of the manometric catheter must cover approximately 30 cm for most subjects, and in some cases (e.g., a very tall subject or a dilated esophagus due to achalasia) it may not be possible to measure simultaneously across the whole region, and data may be lost from the upper sphincter (which is not generally a problem for clinical studies). In this situation, where such data is relevant, a series of

swallows may need to be repeated with the catheter repositioned so that the sensors are appropriately placed to record data from the segment that was missed. All current HRM systems record over 31–35 cm, the spacing of sensors is limited to some degree by the physical nature of the sensors, currently making placement at <1 cm intervals impractical for solid-state systems. Although water-perfused systems can have more closely spaced sideholes, as the total number of perfusion channels is limited by the number of channels within the extrusion, this comes at the expense of the length of the recording area of the catheter. Although ideally, recordings would be made with as small an intersensor distance as possible, and it is uncertain what the minimal interchannel distance is to diagnose esophageal motor disorders, the Chicago Classification criteria have been developed for catheters with sensors spaced at 1 cm intervals. For example, in the Chicago classification, a weak contraction is defined as a pressure break of more than 2 cm at the 20 mmHg isobar which cannot reliably be detected with pressure sensors spaced at any more than 1 cm intervals. Moreover, detection of hiatus hernia and visualization/measurement of dynamic changes at the lower esophageal sphincter (LES) (e.g., descent of the diaphragm with inspiration, movement of the LES) cannot be accomplished with sensors spaced at more than 1 cm.³

A number of extra functions are available in some systems to record additional data to correlate the position of esophageal contents with esophageal pressure patterns. Both water-perfused and solid-state manometry catheters are available in combination with impedance monitoring segments, allowing simultaneous measurement of intra-esophageal impedance with pressures (HRIM). Alternatively, in some systems, it is possible to connect video-fluoroscopy systems to HRM data recorders so that images of bolus position can be recorded together with the pressure data.

PROTOCOL

Equipment preparation

Before arrival of the subject, the equipment is prepared for use by setting up the recording system and performing a calibration if required.

Preparations for solid-state system recordings involve connecting a clean catheter to the recording system and checking that the sensors are functioning correctly. A two point calibration is performed in a pressure chamber or pressure tube. If a sanitary sheath

is used during the measurement, the calibration is performed with the catheter in the sheath.

Preparation of water-perfused systems is more complicated than solid-state systems. Initially, the perfusion reservoir and pump are filled with water and the reservoir is pressurized to drive flow through the capillaries, with the water-channels opened to check that all channels are perfusing. As the transducers do not change their electrical characteristics significantly between studies and the same transducers are used on each occasion, a gain calibration is not required for each study, however, pressure offsets must be referenced to atmospheric pressure to account for hydrostatic and perfusion pressure offsets prior to each study. When required, a two point calibration can be performed with a perfused catheter attached and placed in a pressure chamber or tube (as for the solid-state system), or by raising the catheter by a known distance (taking advantage of the hydrostatic effects of the water column). Alternatively, the gains can be calibrated by applying two known pressures directly to the transducers without a catheter attached. The function of the catheter and recording system can be tested by lifting the catheter up 30–50 cm; pressure in all channels should increase in a similar extent. After initial setup, the catheter should be perfused with water for several minutes prior to use to ensure that the pressures are stable. Unstable pressures have a number of causes; the most common is residual bubbles in the recording system which may respond to flushing with a syringe. Other potential problems include blockage of a capillary by particles (if the water used for perfusion is not adequately filtered), leakage from a connection or cracked component, running out of water or 'drift' in pressures due to changes in the reservoir pressure. Staff using perfusion manometry need to be trained to recognize and deal with these problems in order for recordings to be technically adequate.

Immediately before each study, recording channels are referenced to atmospheric pressure by placing the

Table 1 Characteristics of solid-state and water-perfused manometry

	Solid-state manometry	Water-perfused manometry
Costs	High	Low
Preparation	Easy	More time consuming
Location of transducers	Within catheter	External
Autoclave possible	No	Yes
Pressure rise rate	Very high	Medium

catheter in the horizontal position at the level of the subject, and activating the zero referencing function of the software. If the measurement is to be performed in the upright or semi-supine position, the catheter is referenced in that position at the level of the subject's esophagus.

Subject preparation

Medications and other drugs (including nicotine) that influence upper gastrointestinal motility are stopped in advance, if possible. Subjects are fasted prior to the study with a similar protocol to that used locally for upper endoscopy. In subjects with suspected achalasia, a liquid diet may be advised for one or more days before the measurement. The purpose of keeping the subject fasted is mainly to reduce the chance of vomiting and aspiration during intubation of the catheter, although the presence of food in the stomach and small intestine also has physiological effects on the LES.

The prospect of nasogastric intubation with a catheter can cause significant anxiety and careful education and instruction will improve cooperation and tolerance of the procedure. Subjects should be informed that they may experience minor discomfort in the nose and throat (which can be reduced by the use of a local anesthetic spray) as well as some possible gagging during introduction of the catheter, but will be able to breathe and speak normally when the catheter is in place. Occasionally, a vagal reaction or collapse occurs (particularly during introduction of the catheter), and staff must be prepared for this possibility. Damage to the nose, pharynx or esophagus is a rare possibility. Verbal consent should always be obtained and written informed consent may be required in some countries.

Introduction of the catheter

High-resolution manometry catheters are generally placed through the nares, although placement through the mouth is also possible. Placement through the nares is preferred as it is less uncomfortable and reduces the risk of damage to the catheter by biting. In addition, transnasal manometry allows direct measurement of the position of the LES with respect to the nares, which is required if subsequent pH-impedance monitoring is to be performed. The catheter is introduced with subject in sitting position with water available, and nasal/pharyngeal topical anesthesia if this is to be used. The catheter is lubricated and slowly introduced through the nares (it is often helpful to ask the subject whether one side of the nose is blocked so that it can be avoided), and over the floor of the nasal

cavity. As the floor of the nasal cavity runs directly posteriorly, the tip of the catheter should be aimed in the direction of the ears and not upwards in the direction of the bridge of the nose. Occasionally, the tip of the catheter impacts in the posterior pharyngeal wall, which can be uncomfortable for the subject. This can be remedied by gentle manipulation/rotation or reshaping of the catheter, occasionally the other nare must be used. After 10–15 cm, the catheter will be in the hypopharynx and just above the upper esophageal sphincter. Further introduction will cause a gag reflex or coughing, which can be reduced by the subject being asked to swallow during passage of the catheter through the lower pharynx and UES. The subject is given a cup of water with a straw and is asked to take sips and swallow continuously with his/her chin down while the catheter is introduced through the sensitive area. Subjects often need to pause at this point to catch their breath, but once the catheter is through the UES, it will generally then pass easily to the stomach with minimal resistance. If the subject coughs severely during the pharyngeal phase of the insertion, passage into the larynx should be suspected and the catheter withdrawn. If significant resistance is encountered, the catheter should not be forced as this may cause damage, particularly if the tip is impacted in a diverticulum. If difficulty is encountered in the esophagus (e.g., in achalasia), it is often effective to pull the catheter back to the proximal esophagus, change the subject's position (e.g., try lying on one side or another) and then reintroduce the catheter. Occasionally, fluoroscopy is required to pass the catheter, and rarely the catheter needs to be positioned under endoscopic visualization. Following passage across the LES, the catheter is introduced well into the stomach and pulled back to the recording position to remove any bends in the catheter caused during the introduction, thereby ensuring that distances recorded from the nares are accurate. The catheter is positioned while viewing the pressure data on the computer screen and adjusting the position of the catheter.

The catheter is positioned correctly when both the UES and LES can be recognized and when at least two pressure sensors are located in the stomach (or below the diaphragm in the case of hiatus hernia). The LES is recognized by following the pressure wave associated with swallowing, as the LES is always continuous with the termination of the swallow. In case of a very weak LES pressure, this may be recognizable only during the LES after-contraction that usually follows a swallow. In the case of very weak or absent peristalsis and a weak LES, it may not be possible to locate the LES based on pressure data. The position of the diaphragm

can be determined by examining the data for the pressure inversion point (PIP). During inspiration, pressure in the thorax decreases while pressure in the abdomen increases. The point where the pressure changes with respiration meet is called the pressure inversion point; this is generally located at the level of the diaphragm.⁴ The PIP becomes more obvious when the subject is asked to inspire deeply, and descent of the diaphragm is also seen.

Following placement of the catheter, the subject is asked to lie down. Although the upright position is more physiological in terms of swallowing, there are differences in peristalsis when upright data are compared with supine data,⁵⁻⁷ and normal values for HRM and the Chicago Classification have been developed based on data recorded in the supine position. Moreover, independent of whether a solid-state or water-perfused catheter is used, when a column of water forms in the esophagus in the upright position, hydrostatic effects become relevant to esophageal emptying. This may be seen due to a relative obstruction at the gastro-esophageal junction, for example, in patients with achalasia. Nevertheless, some subjects find it difficult or impossible to tolerate lying down or to swallow in the supine position, and occasionally artifacts are seen (presumably due to compression by surrounding structures e.g., left lobe of the liver), such that it may be preferable to perform the study with the subject sitting and analyze the data in that context. Normal values have also been described for measurements in upright position.⁶

After the subject is placed in supine position and the catheter is correctly positioned, the subject should be allowed several minutes to accommodate to the catheter, and allow the sensors in a solid-state catheter to warm. Once the subject is comfortable, basal recordings of the LES are obtained for several minutes if possible. During the basal recording, subjects should be instructed to swallow as infrequently as possible and to breathe quietly and regularly.

Standard evaluation of esophageal motility is performed using 10 swallows of 5 cc of water in the supine position, and this should be considered to be the minimum. The value of extra swallows and changes in position has not been extensively evaluated, but may provide more information. Tap water can be used but when pressure measurement is combined with impedance monitoring, saline is used to enhance contrast on the impedance measurement. Swallows should be recorded at approximately 20–30 s intervals so that the peristaltic wave has terminated and the LES pressure has returned to baseline. If the subject

swallows again before the next swallow is due, an extra period is added to avoid swallow-induced suppression of esophageal contractility.⁸ After the 10 swallows have been recorded, the measurement can be terminated and the catheter removed. Note that pull-through techniques are not required with HRM, as multiple sensors allow simultaneous monitoring of the entire esophagus and both sphincters. After the procedure, for solid-state systems, temperature compensation is performed, and for water-perfused systems, a short period of recording is made to ensure that channels have not drifted during the study.

Even if all preparations have been performed correctly and the protocol has been followed, measurements occasionally fail. An analysis of 2000 routine solid-state HRM studies showed that of 414 measurements (20.7%) were considered technically imperfect. Most frequently, this was because of insufficient numbers of interpretable swallows (249 measurements, 12.5% of total), the LES was not traversed (110 measurements, 5.5% of total) or there were problems with sensor or thermal compensation afterwards (28 measurements, 1.4% of total).⁹

Contra-indications for esophageal manometry

Although manometry is in general a very safe procedure, there are some small risks and contra-indications. Issues related to passage of the catheter are described in the previous section. In case of suspected complete or near complete obstruction, manometry is contraindicated (and not likely to be of value in any case) and a barium swallow and/or endoscopy should certainly be performed before attempting manometry. Severe coagulopathy is a relative contra-indication and may cause epistaxis, but serious bleeding is very rare. Cardiac conditions in which vagal stimulation is poorly tolerated or can cause arrhythmias are also a relative contra-indication. No data are available on the risk of bleeding in subjects with esophageal varices, but a cautious approach would be prudent (particularly in the setting of recent bleeding).

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AUTHOR CONTRIBUTIONS

AB and GH performed the research, analyzed the data and wrote the paper.

CONFLICT OF INTERESTS

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REVIEW ARTICLE

Evaluation of the esophagogastric junction using high resolution manometry and esophageal pressure topography

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Abstract

Background The assessment of the esophagogastric junction (EGJ) is the most challenging aspect of clinical esophageal manometry. Although conventional manometric systems can be optimized toward interrogating specific aspects of the EGJ, they are too limited in recording channels and/or fidelity for a comprehensive assessment. The technological advantages inherent in high resolution manometry (HRM) with esophageal pressure topography (EPT) analysis substantially change this equation providing a technology sufficiently robust to dynamically record the contractile activity within the EGJ with both good fidelity and good spatial resolution.

Purpose This review is an update on our understanding of the application of HRM and EPT to the analysis of EGJ function. With respect to sphincter relaxation, the integrated relaxation pressure (IRP) has proven to be a robust metric in differentiating intact from impaired EGJ relaxation. In the process, it revealed that impaired EGJ relaxation could occur not only in the setting of achalasia but also with other causes of EGJ outflow obstruction including hiatus hernia. The morphological description of the EGJ by EPT has also revealed not only a spectrum of ab-

normality ranging from an intact sphincter to overt herniation, but also the surprise finding of spontaneous conversion among sphincter configurations, emphasizing its dynamic nature. With respect to barrier function, preliminary data have refocused on the crural diaphragm as a key-differentiating feature between preserved and compromised function. Finally, although the accomplishments summarized above are substantial, much work remains to fully exploit the potential of EPT in the clinical characterization of the EGJ.

Keywords esophagogastric junction, gastro-esophageal reflux disease, lower esophageal sphincter, manometry.

Abbreviations: CD, crural diaphragm; EGJ, esophagogastric junction; GERD, gastro-esophageal reflux disease; HRM, high resolution manometry; LES, lower esophageal sphincter.

INTRODUCTION

The esophagogastric junction (EGJ) is the focal point for considerable esophageal pathophysiology, be it in the domain of gastro-esophageal reflux disease (GERD) or esophageal motility disorders. Esophagogastric junction incompetence is the most fundamental determinant of GERD. Impairment of neural control over the EGJ is the feature by which achalasia was named from the Greek, 'not loosening' (khalasis). Consequently, the assessment of EGJ competence and relaxation is a central aim of clinical manometry testing. However, several inherent attributes of EGJ pressure complicate its manometric assessment: (i) intraluminal pressure

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recorded within this region can be influenced by crural diaphragm (CD) contraction¹ (which varies substantially with the respiratory cycle), (ii) lower esophageal sphincter (LES) contraction, the spatial relationship between the CD and the LES (potentially ranging from completely superimposed to completely disassociated),² and (iii) the radial orientation of the sensor within the lumen which characteristically exhibits substantial radial pressure asymmetry.³ Hence, it is not surprising that the goal of defining manometric metrics for a normal or dysfunctional EJJ has proven elusive.

High resolution manometry (HRM) with esophageal pressure topography (EPT) has the potential to overcome some of the limitations of EJJ manometrics experienced with earlier technologies. The basic concept of HRM is that by vastly increasing the number of pressure recording sites and decreasing the spacing between them, one can monitor intraluminal pressure without spatial gaps between recording sites.^{4,5} This feature overcomes two major limitations of conventional manometric recording: (i) the need to compensate for axial motion of sphincter elements with the use of a 'sleeve' device in the assessment of EJJ relaxation and (ii) the need to suspend respiration during a 'pull-through' assessment of the axial pressure profile within the EJJ. With HRM, EJJ pressure is dynamically monitored during normal respiration with defined axial resolution (usually 1 cm) and without artifacts attributable to swallow-induced sphincter movement⁵ or to EJJ conformational changes that may spontaneously occur.⁶ However, even within the domain of EPT, there are still a number of variables regarding the methodology for assessing EJJ relaxation, morphology, and competence (barrier function). Progress in the understanding of the optimal methodology for assessing the EJJ among these functional domains has been considerable with the widespread adoption of HRM into clinical practice. This review is organized as an update of this progress in each of these three areas.

EJJ RELAXATION

Abnormal swallow-induced LES relaxation is a key element in defining achalasia. As such, the assessment of LES relaxation is a major objective of clinical manometry studies. Several nuances of quantifying LES relaxation emerge in EPT.^{5,7} Firstly, it is too simplistic to think of EJJ relaxation pressure as reflective only of LES relaxation. At any one instant, the pressure measured within the region of the EJJ is the greatest of three potential contributors: LES

pressure, CD contraction, and intrabolus pressure as the swallowed water traverses the EJJ.⁵ Secondly, the CD is superimposed on the LES and swallowing does not inhibit CD contraction, which continues through the period of deglutitive LES relaxation.^{8,9} Consequently, other than in instances of hiatal hernia with complete axial separation between the LES and CD, one is actually measuring EJJ relaxation, not LES relaxation. Thirdly, swallow-induced peristalsis with contraction of the longitudinal muscle results in an average of 2 cm proximal migration of the LES.¹⁰ In extreme instances, this sphincter movement can be 9 cm.¹¹ It has long been recognized that a single manometric sensor positioned within the sphincter prior to swallowing will end up within the stomach during swallow-induced esophageal contraction creating the artifact of 'pseudorelaxation'.⁷ For all of these reasons, 'nadir LES pressure' as applied in conventional manometry, is a poor measure of incomplete deglutitive EJJ relaxation. Recognition of these deficiencies led to the development of a new EPT metric; the Integrated Relaxation Pressure (IRP).⁷ The IRP is measured within the spatial domain necessary to capture the axial movement of the LES in the post-swallow period and spans the time from deglutitive upper sphincter relaxation until cessation of the distal peristaltic contraction (or 10 s in the absence of peristalsis). Thus, the IRP is similar to measuring EJJ relaxation with a Dent sleeve with the added stipulation that the number being reported is the average value for the 4 s of maximal relaxation after the swallow (Fig. 1). Table 1 illustrates improvement in the detection of impaired EJJ relaxation when IRP is

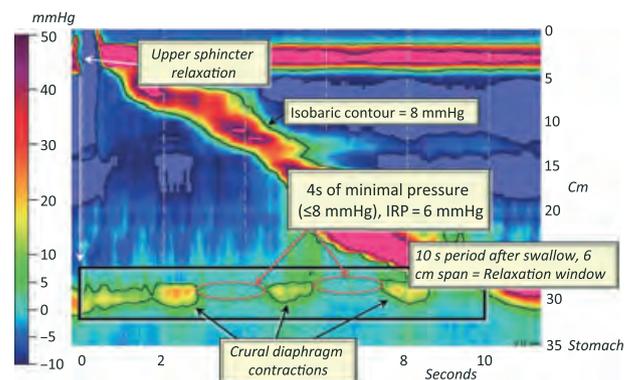


Figure 1 Graphical description of the derivation of the IRP. The relaxation window occurs for the 10 s period after the swallow and spans across the EJJ. The isobaric contour tool is used to find the pressure at which there is a 4 s gap in the EJJ pressure band. E-sleeve measurements are then taken within this 4 s period and the IRP is the average of those measurements, 6 mmHg in this case.

Table 1 Comparison of EGJ relaxation measures in 62 achalasia patients. The nadir pressure in conventional terms was the lowest pressure recorded from the sensor centered in the EGJ at the onset of the swallow, whereas the nadir EPT pressure accounted for sphincter movement after the swallow, in essence a nadir sleeve pressure. Both exhibited very poor sensitivity for detecting achalasia because of the subset of achalasics with brief periods of EGJ relaxation to within the normal range. On the other hand, the IRP requires persistence of EGJ relaxation for 4 s, skipping periods of CD contraction if necessary. Normal values were determined from 75 control subjects. Adapted from [7]

EGJ relaxation metric	Achalasia sensitivity %	False positives %	False negatives %
Nadir pressure, conventional (≥ 7 mmHg)	52	0	48
Nadir EPT pressure (≥ 10 mmHg)	69	0	31
Integrated relaxation pressure (≥ 15 mmHg)	97	0	3

compared with the 'nadir LES pressure' in a series of achalasia patients. This is important because failing to detect impaired EGJ relaxation in these patients would result in giving them an alternative diagnosis, most commonly misclassifying them as ineffective esophageal motility or DES.¹²

The data detailed in the preceding paragraph were obtained using the Sierra (now Given Imaging) solid-state high resolution manometry assembly. This device uses unique pressure transduction technology (TactArray™, Given Imaging, Los Angeles, CA, USA) that allows each of the 36 pressure sensing elements to detect pressure in each of 12 radially dispersed sectors. The sector pressures are then averaged, making each of the 36 sensors a circumferential pressure detector with the extended frequency response characteristic of solid-state manometric systems.¹² Among available technologies, the Sierra approach of averaging the electrical signal from 12 radially dispersed independent pressure sensors is unique. Ultimately, signal averaging may not prove to be the optimal approach as a strong argument can be made for preferentially reporting the lowest sector pressure. However, the Sierra device is currently the only device for which normal values of IRP have been published and whose performance has been tested clinically in the detection of achalasia, a key clinical application.⁷ Consequently, practitioners are cautioned against assuming that the same normative values and the 15 mmHg IRP threshold for the detection of impaired EGJ relaxation necessarily apply to other devices, be they from Given Imaging or other manufacturers.

Although utilizing the IRP in the EPT analysis of EGJ relaxation goes a long way toward clarifying the diagnosis in many achalasia patients that would otherwise be classified as 'non-specific' or misclassified to a non-achalasia diagnosis, there remains a group of patients with impaired EGJ relaxation failing to meet criteria for achalasia due to some preserved peristalsis. A series of 1000 consecutive patients studied with EPT

included 16 such individuals with what has been termed 'EGJ Outflow Obstruction' exhibiting not only an IRP greater than 15 mmHg but also preserved peristalsis and elevated intrabolus pressure above the EGJ during peristalsis.¹³ The finding of an elevated intrabolus pressure proximal to the sphincter is important because it validates the physiological significance of impaired EGJ relaxation. From a physiological perspective, elevated intrabolus pressure is the consequence of the impaired relaxation. Recent work suggests that when EGJ outflow obstruction occurs as a consequence of incomplete relaxation, it is accompanied by a relative increase in the ratio of peristaltic amplitude in S3 vs S2, whereas this is not the case with mechanical obstruction.¹⁴ Nonetheless, EGJ Outflow Obstruction encompasses a heterogeneous group of patients with some individuals having an incomplete phenotype of achalasia and others probably having an undetected mechanical cause of EGJ outflow obstruction such as hiatus hernia, esophageal stenosis, or eosinophilic esophagitis. Consequently, it is a patient group that merits further evaluation with mucosal biopsies and imaging studies to exclude inflammatory or malignant etiologies, be that with computerized tomography or endoscopic ultrasound. Only after these possibilities have been fully explored should it be accepted as atypical achalasia.

Among the 16 patients with idiopathic EGJ Outflow Obstruction described in the previous section, three were noted to have hiatus hernias. In one of these instances, it was the crural diaphragm rather than the LES that appeared to be the focus of resistance to bolus transit, suggesting this be the cause of dysphagia. A subsequent report specifically focused on EGJ relaxation characteristics of patients with sliding hiatus hernia and dysphagia by selectively restricting the IRP measurement boundaries to the LES and crural diaphragm individually.¹⁵ A subset of 10 patients was found exhibiting a relative obstruction at the crural diaphragm with elevated intrabolus pressure extending

through the LES, supporting the concept that sliding hiatus hernia could be responsible for dysphagia. Consequently, patients presenting with elevated EGJ relaxation pressure in the context of a small hiatus hernia require careful analysis of the discrete elements of the EGJ before making a diagnosis of achalasia.

Another complexity of the IRP measurement is in how to deal with recordings from patients with large hiatal hernias. With large hiatal hernias, there is complete separation between the LES and CD and also the potential that the distal end of the recording assembly did not cross the CD to gain exposure to sub-diaphragmatic intragastric pressure. Among a series of 2000 EPT studies, this difficulty was encountered in 63/111 (57%) of patients with a large hiatal hernia (at least 5 cm on EGD examination).¹⁶ The consequence of this is that the IRP cannot be accurately calculated as the intra-hernia pressure can be significantly lower than the intra-abdominal pressure causing a falsely elevated IRP. This would have led to a false positive diagnosis of achalasia in 3 of the 63 cases alluded to in the series above if the problem related to the large hernia were not recognized. In the setting where manometric data is key to clinical decision-making, placing the catheter endoscopically can usually overcome the problem.

As alluded to above, it is not possible to measure the IRP if the manometric catheter fails to traverse the EGJ. This can occur not only in the setting of hiatus hernia as just discussed but also in achalasia. In a 2000 patient series, this problem was encountered in 28 achalasia patients.¹⁶ However, although not optimal, 94% of these studies were still judged diagnostic of achalasia based on the observed patterns of esophageal pressurization and associated endoscopic data.

EGJ MORPHOLOGY

The conventional manometric assessment of EGJ competence has focused on LES pressure and length characteristics. Reflecting the diverse manometric methodology applied to sphincter measurements, there is no widely accepted convention on how to make these measurements.^{17,18} As an indication of disease severity and prognosis, not surprisingly, measurements of LES pressure have not proven terribly useful in the diagnostic assessment of GERD. The adoption of EPT has the potential to improve upon the limitations and clinical utility of LES pressure and length measurements. For example, EGJ pressure morphology can be dynamically monitored in a consistent fashion with normal respiration and with minimal movement-related artifact. Not only peak EGJ pressure but also

the relative positions and vigor of the LES and CD components are definable. Considerable further work is necessary, however, to establish standardized measurement techniques and clinical correlations.

The spectrum of EGJ pressure morphology in EPT during normal respiration was described in a series of 75 control subjects and 156 patients undergoing evaluation for GERD.¹⁹ Inspiratory EGJ pressure was defined as the maximal or peak pressure occurring during the normal respiratory cycle. Expiratory EGJ pressure was defined as the pressure at the midpoint between adjacent inspirations with all EGJ pressures referenced to intragastric pressure. The respiratory inversion point (RIP) was localized as the axial position along the lumen of the EGJ at which the inspiratory EGJ pressure became less than the expiratory EGJ pressure. Conceptually, this is the position at which the external EGJ environment switches from intra-abdominal to intra-mediastinal pressure. The inspiratory augmentation of EGJ pressure was the difference between basal inspiratory pressure and basal expiratory pressure. This could have a positive or negative value.

Using both isobaric contour plots and spatial pressure variation plots, the EGJ could be classified into three subtypes based on the axial relationship between the maximal EJJ pressure peak and the CD pressure peak. When there was a double-peaked EGJ pressure profile on an isobaric contour or spatial pressure variation plot during inspiration, the proximal peak was taken to be the LES and the distal peak to be the CD. The LES-CD separation was the distance separating the peaks at inspiration. With EGJ Type I, there is no discernible LES-CD separation because the CD was superimposed on the LES (Fig. 2). With a Type I EGJ, the EGJ pressure band often appears to move up and down with the respiratory cycle, suggesting that the LES and CD are tethered to each other, presumably by the phrenoesophageal ligament. With a Type II EGJ, there is minimal, but discernible, LES-CD separation making for a double-peaked pressure profile on the spatial pressure variation plot. However, the nadir pressure between the LES and CD peaks is still greater than gastric pressure (Fig. 2). Type II EGJ is not associated with hiatus hernia, but represents an intermediate condition in which LES-CD separation was >1 cm and <2 cm. With a Type II EGJ, respiratory movement, the EGJ pressure band is less apparent than with Type I, presumably because of laxity of the phrenoesophageal ligament. With a Type III EGJ, there is more than 2 cm LES-CD separation at inspiration (Fig. 2). This is the HRM signature of hiatus hernia. Two subtypes were discernible, IIIa and IIIb, with the distinction being that the respiratory inversion point is

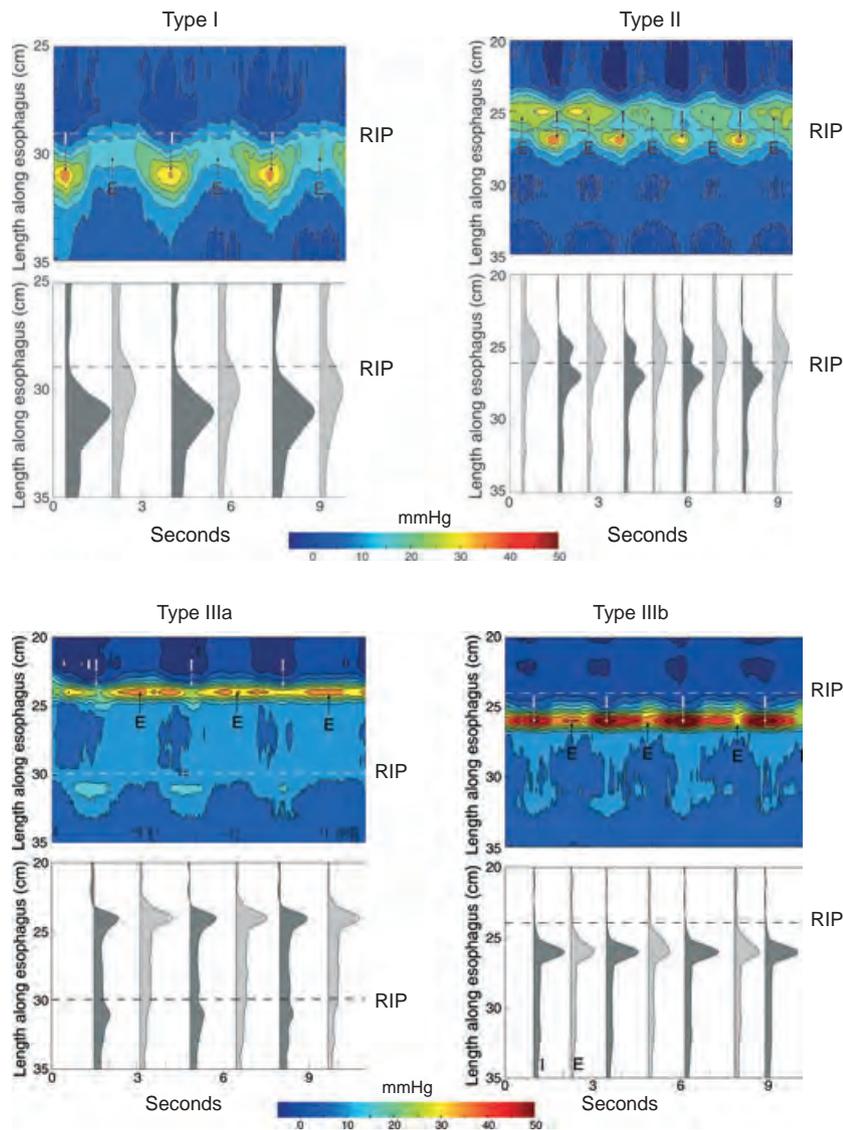


Figure 2 Examples of EGJ pressure morphology subtypes primarily distinguished by the extent of LES-CD separation. The upper plot in each panel is an EPT plot spanning from the distal esophagus, across the EGJ, and into the proximal stomach during several respiratory cycles with the pressure magnitude corresponding to spectral colors (scale at bottom). The location of the respiratory inversion point (RIP) is shown by the horizontal dashed line. The lower plot in each panel illustrates a series of spatial pressure variation plots at the instants of peak inspiration (dark gray) and mid-way between inspirations (light gray) corresponding to the times marked I and E on the upper panels. With Type I, there is complete overlap of the CD and the LES with a single pressure peak in the spatial pressure variation plots during both inspiration and expiration. With Type II, the EGJ is characterized by 1–2 cm LES-CD separation making for a double-peaked spatial pressure variation plot, but the nadir pressure between the peaks was still greater than gastric pressure. The RIP is within the EGJ at the proximal margin of the CD. The EGJ type III was defined when LES-CD separation was >2 cm at inspiration. Two subtypes were discernible, IIIa and IIIb, with the distinction being that the respiratory inversion point was distal to the LES with IIIa and proximal to the LES in IIIb.

distal to the LES with IIIa and proximal to the LES in IIIb. Thus, inspiratory ‘augmentation’ of EGJ peak pressure often has a negative value with type IIIa but, by definition, is positive with IIIb.

An important consequence of these observations with respect to EGJ pressure morphology is that the

EGJ morphology is dynamic and varies with time and activity, especially eating. Prolonged HRM recordings in patients with endoscopically demonstrated hiatal hernias revealed them to exhibit both Type I and Type II EGJ morphology and to migrate between conformations within the same study.^{6,20} Consumption of a

liquid meal was associated with conversion from a Type II profile to a Type I profile for the subsequent 60–90 min.²⁰ Similarly, three hour postprandial recordings in 16 patients with small hiatal hernias on endoscopy found a Type I profile 57% of the time and a Type II profile for the remainder of the recording.⁶

EGJ BARRIER FUNCTION

Impaired EGJ barrier function leading to excessive reflux of gastric juice into the distal esophagus is the root cause of GERD. Reflux occurs as discrete events that can ultimately be attributed to LES hypotension overcome by abdominal straining or transient LES relaxations (TLESRs). However, most patients with GERD have normal LES pressure at rest and a normal frequency of TLESRs. Presumably, what sets them apart from control subjects is physiological dysfunction of the EGJ when faced with everyday challenges manifest by liquid reflux. A recent study compared EPT attributes of the EGJ of 75 asymptomatic controls to 156 patients whose GERD status was characterized by endoscopy and pH monitoring in an attempt to ascertain the most relevant variables. All patients reported a similar severity of GERD symptoms, but were categorized as EGD+ if they had esophagitis on endoscopy and pH+ if they had excessive esophageal acid exposure or a positive reflux-symptom association on an ambulatory esophageal pH monitoring study. The EGJ was characterized by morphology (Type I, II, IIIa, IIIb), LES-CD axial separation, inspiratory pressure, expiratory pressure, and magnitude of inspiratory pressure augmentation. The respiratory effects on EGJ pressure morphology among subject groups are summarized in Table 2. Mean LES-CD separation was similar between control subjects and EGD-/pH- patients. In contrast, EGD+ patients and EGD-/pH+ patients had significantly greater LES-CD separation. Moreover, as evident in Table 2, there was a significant difference in the expiratory EGJ pressure between controls and GERD patients. Furthermore, EGD+ and EGD-/pH+ patients had a significantly lower inspiratory EGJ augmenta-

tion when compared with asymptomatic controls or EGD-/pH- patients.

Although Table 2 suggests that multiple EPT metrics differentiated the GERD from non-GERD patients, these measurements are, to some degree, interdependent. Thus, logistic regression analysis was performed to prioritize potential manometric measures as independent variables using GERD as a categorical dependent outcome. End-expiratory EGJ pressure, LES-CD separation, and inspiratory EGJ augmentation were all significantly associated with GERD when controlling for age and BMI. However, a model that examined all EGJ parameters simultaneously while controlling for age and BMI revealed that inspiratory augmentation, BMI and age were the only variables with a statistically significant *independent* association. The parameter estimate for inspiratory augmentation was -0.07 (SE 0.03, $P = 0.001$) while those for age and BMI were 0.08 (SE 0.04, $P = 0.04$) and 0.13 (SE 0.03, $P < 0.001$), respectively.

The logistic regression analysis described in the previous section suggests that the only manometric variable independently associated with GERD as the dependent outcome was the magnitude of inspiratory augmentation of EGJ pressure. As a group, EGJ type III subjects had significantly less inspiratory augmentation compared with EGJ types I or II. Only nine EGJ type I subjects had a zero or negative value of inspiratory augmentation and all of these had either a positive EGD or a positive pH study. Furthermore, 25 of 27 of the EGJ type III subjects with zero or a negative value of inspiratory augmentation had either a positive EGD or a positive pH study. ROC analysis of the sensitivity and specificity for inspiratory EGJ augmentation as a predictor of pH or endoscopy positive GERD revealed that the specificity was 95% or better if the inspiratory augmentation was less than or equal to 4 mmHg. However, the sensitivity at that threshold was only 34%. The optimal cut point value for inspiratory augmentation was 10 mmHg with a sensitivity of 57% and specificity of 79%. The inter-relatedness among inspiratory augmentation, EGJ morphology subtype and GERD status is illustrated in Fig. 3. The

Table 2 LES-CD separation and EGJ pressure profile amongst control subjects and symptomatic patients subgrouped by objective measures of GERD (EGD, pH monitoring). Data from Pandolfino *et al.* [18]

	Controls	EGD (-)/pH (-)	EGD (-)/pH (+)	EGD (+)
LES-CD separation (cm)	0.2 (0.1)	0.4 (0.2)	0.9 (0.2)*	1.2 (0.2)*†
Expiratory EGJ pressure (mmHg)	24.0 (1.1)	20.5 (2.7)	18.6 (1.9)*	16.8 (1.2)*
Inspiratory EGJ augmentation (mmHg)	16.9 (1.0)	16.7 (2.1)	11.5 (1.9)*†	10.0 (1.2)*†

ANOVA, * $P < 0.05$ vs controls, † $P < 0.05$ vs EGD (+).

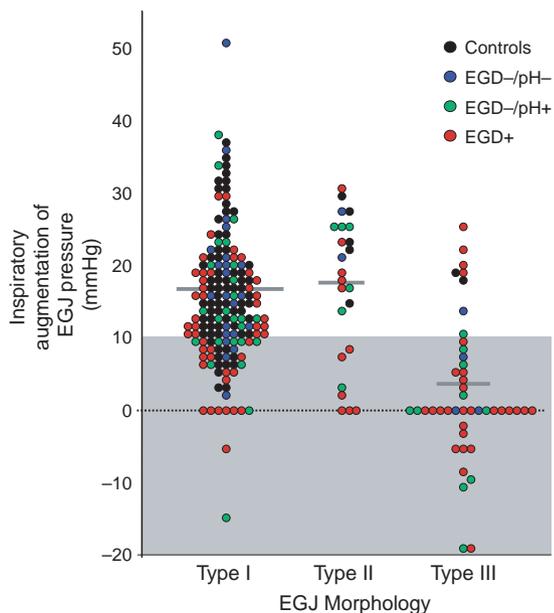


Figure 3 Individual data on inspiratory EGJ augmentation of EGJ pressure with individuals characterized both by EGJ subtype and GERD status. EGJ morphology type III subjects had a significantly lower mean inspiratory EGJ augmentation than types I and II (ANOVA, $P < 0.05$). Thirty-seven of the 39 subjects with an inspiratory augmentation ≤ 0 had either a positive EGD or positive ambulatory pH study.

shaded area of the Figure indicates depicts the group with an inspiratory augmentation of less than 10 mmHg, 79% of whom were in the GERD positive population. It should be recognized, however, that both the nature of high resolution pressure averaging methodology and the lack of standardized EGJ measurement techniques may contribute to the fact that EGJ characteristics were not more strongly associated with GERD.

Anatomical EGJ variables were also shown to be important during postprandial HRM recordings of 16 GERD patients with small hernias.⁶ In all patients, both single and double pressure profiles were observed with the prevalence of the double-peak profile ranging between 11% and 91% of the total time in individual patients. Fluoroscopic images of the relationship between an endoclip on the squamocolumnar junction and the diaphragm confirmed that the double peak profile was indicative of a hernia configuration. Reflux episodes, detected by impedance pH monitoring, were significantly more frequent in the hernia state (23.1 ± 5.1 per hour) than in the reduced state (12.2 ± 2.4 per hour). Interestingly, the increased reflux episodes were almost uniformly due to non-TLESR mechanisms, especially swallow-induced reflux.

Postsurgical EGJ assessment

The goal of antireflux surgery is to restore an anatomic and functionally competent gastro-esophageal barrier. Surgical techniques aim to correct diaphragmatic crural defects, re-establish an intra-abdominal esophageal segment, and enhance the pressure and length of the neo-high pressure zone at the EGJ via the extrinsic effects of the fundic wrap. Recent studies suggest that high resolution manometry and EPT may prove to be a significant advance over conventional manometry in dissecting out the complex functional alterations in the normal and abnormal postsurgical EGJ.

High resolution manometry has been used to assess the effects of both partial (Belsey) and complete (Nissen) fundoplication on TLESR frequency and EGJ pressure profiles in 20 postoperative patients.²¹ The EGJ pressure profile was minimally affected by partial fundoplication whereas Nissen fundoplication significantly increased nadir EGJ pressures. Whether the technique and/or geometry of the fundoplication affects nadir EGJ pressures remains unknown. This same group of investigators further assessed pre- and post-fundoplication EGJ dynamics and bolus transport in 12 patients using concurrent HRM and fluoroscopy. EGJ lengths were significantly increased, opening diameter decreased (0.6–1.0 cm) and nadir EGJ relaxation pressures were significantly greater following fundoplication. A greater intrabolus pressure was also seen postfundoplication. Finally, EGJ transit time significantly correlated with dysphagia scores postfundoplication. The increase in resistance in flow as a consequence of altered EGJ dynamics postoperatively resulted in significantly prolonged transit times for both liquid and solid bolus swallows.²² These preliminary studies suggest that HRM holds significant promise in the clinical and manometric assessment of both asymptomatic and symptomatic patients post antireflux surgery.

SUMMARY AND FUTURE DIRECTIONS

Historically, the assessment of the EGJ has been the most challenging aspect of clinical esophageal manometry. In part, this is because a comprehensive clinical assessment entails evaluation of sphincter morphology, barrier function with respect to GERD and deglutitive relaxation that is of fundamental importance in the diagnosis of esophageal motor disorders. Although conventional manometric systems can be optimized toward achieving any one of these objectives, they were simply too limited in recording channels and/or fidelity to accomplish all. Further-

more, optimizing the system in one domain typically compromised it in the others. The technological advantages inherent in HRM with EPT analysis have substantially changed this equation and for the first time provided a technology sufficiently robust to dynamically record the contractile activity within the EGJ with both good fidelity and good spatial resolution. However, with this new technology came new challenges, one of which was revising the criteria of manometric analysis to fit the new technology.

Considerable progress has been made in applying EPT to EGJ analysis. With respect to sphincter relaxation, the IRP has proven to be a robust metric in differentiating intact from impaired EGJ relaxation. In the process, it has come to light that impaired EGJ relaxation can occur not only in the setting of achalasia but also with other causes of EGJ outflow obstruction including hiatus hernia. The morphological description of the EGJ by EPT has also revealed not only a spectrum of abnormality ranging from an intact sphincter to overt herniation but also the surprise finding of spontaneous conversion among sphincter configurations emphasizing its dynamic nature. Finally, with respect to barrier function, preliminary data have refocused on the CD as a key differentiating feature between preserved and compromised function.

Although the accomplishments summarized in the previous section are substantial, much work remains

to fully exploit the potential of EPT in the clinical characterization of the EGJ. In particular, the significance of morphological subtypes and CD function as they pertain to GERD has only barely been explored. GERD is the major cause of upper gastrointestinal morbidity in Western society and it is fundamentally a physiological disturbance of the EGJ. Nonetheless, prior to the introduction of HRM, the manometric evaluation of the EGJ provided minimal insight into characterizing its dysfunction. This robust technology, and future evolutions thereof, surely will finally reveal some of these secrets.

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There are no financial or professional disclosures relevant to the synthesis of this paper for either of the authors.

AUTHOR CONTRIBUTIONS

PJK performed the initial literature search, wrote the initial draft of the paper and managed the integration of coauthor contributions; JHP assisted in critiquing, editing, and refining the paper.

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REVIEW ARTICLE

Evaluation of esophageal contractile propagation using esophageal pressure topography

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Abstract

Background High-resolution manometry and esophageal pressure topography have enhanced our ability to analyze esophageal motor disturbances by improving the detail and accuracy of measurements of peristaltic activity.

This has been extremely helpful in the evaluation of disorders of rapid propagation as the technique is able to define important time points and physiologic landmarks that are crucial in defining peristaltic velocity and latency intervals.

Purpose The goal of the current review will be to assess how esophageal pressure topography has impacted our ability to define important phenotypes of rapid propagation. Additionally, this review will also be utilized to complement the description of the Chicago Classification of Esophageal Motor Disorders, which is presented in this supplement issue.

Keywords distal esophageal spasm, esophageal pressure topography, high-resolution manometry.

INTRODUCTION

High resolution manometry (HRM), in and of itself, is an adaptation of conventional manometric hardware that basically incorporates an increased number of pressure sensors spaced closely together. The data

generated by HRM would therefore be displayed as a tracing format similar to what would be utilized for conventional manometric interpretation. The real advance in terms of manometry is primarily focused on the analysis techniques that were derived to optimize the information from high resolution manometry. To better visualize the data, Clouse and Staiano¹ incorporated a process of interpolation or averaging between sensors to display the information in the form of seamless isobaric color regions on esophageal pressure topography plots (EPT) (Fig. 1). The EPT or 'Clouse Plots' have the capacity to convert manometric information into distinct patterns that illustrate the physiology of contractile coordination and the mechanics associated with bolus transit evidenced on combined studies with fluoroscopy and impedance.

This new technique has benefitted our evaluation of esophageal body peristaltic function by improving both the detail and accuracy of measurements of peristaltic function. Firstly, important landmarks can be described that impact measurements of integrity of the wavefront and the pattern of propagation. These landmarks, coupled with the ability to define a space-time domain, greatly improve our ability to define the timing of contractile events and bolus transit through the esophagus and into the stomach. A disruption in the sequencing and order of contraction, as it relates to the timing of EGJ opening, will impair bolus transit and potentially lead to complications, such as discomfort and regurgitation/aspiration. The goal of this manuscript will be to detail how EPT has impacted our ability to measure important components of peristaltic function with a focus on contractile propagation and spastic disorders of the esophagus. Although we will discuss both the physiology and quantitative metrics utilized for assessing contractile vigor, the

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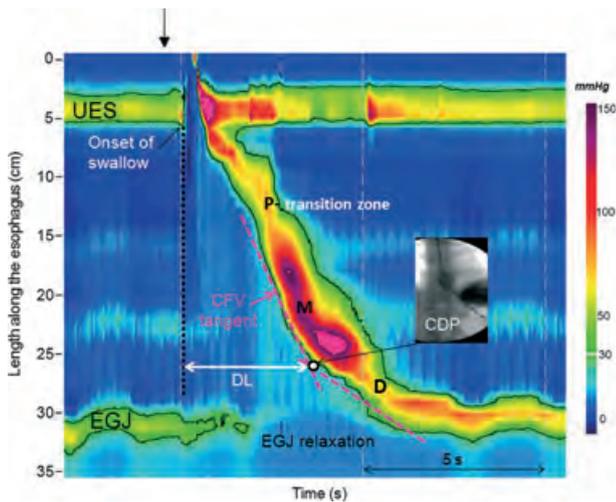


Figure 1 A normal swallow in a Clouse plot. Two high pressure zones are visualized: the upper esophageal sphincter (UES) and the esophago-gastric junction (EGJ). The highlighted black line is the 30-mmHg isobaric contour circumscribing areas with pressure >30 mmHg. The peristaltic esophageal contraction is characterized by three troughs, one proximal (P), one middle (M) and one distal (D). Defects in the proximal trough are labeled as transition zone defects whereas defects in the middle or distal trough can be labeled as being associated with ineffective esophageal motility due to the proximity of the troughs to the 3 and 8 cm locations above the EGJ. The Contractile Deceleration Point (CDP) represents the inflection point in the contractile front propagation. It is localized on Clouse plots by fitting two tangential lines to the initial and terminal portions of the 30-mmHg isobaric contours and noting intersection of the lines (white dot). On fluoroscopic image, it corresponds to the transition to ampullary conformation and slowing of the luminal closure front. The Contractile Front Velocity (CFV) corresponds to the slope of the tangent line to the initial portion of the contraction (between P and the Contractile Deceleration Point). The distal latency (DL) is measured from the onset of swallow (dashed vertical line) to the Contractile Deceleration Point. Modified from the HRM Working Group.

assessment of hypercontractility and weak peristalsis will be covered in greater detail in other sections of this supplement.

ESOPHAGEAL BODY MOTILITY

Swallowing not only induces a contraction wave that progresses down the esophageal body but also triggers a wave of inhibition of the esophageal smooth muscle that precedes the arrival of the peristaltic contraction (deglutitive inhibition), resulting in relaxation of the lower esophageal sphincter and in preparation of the esophageal body to receive the oncoming bolus with minimal distal resistance.^{2,3} Experiments *in vitro* and *in vivo* have shown that a wave of muscle hyperpolarization spreads down the esophageal body preceding the occurrence of

peristaltic contractions.⁴⁻⁷ The initial hyperpolarization of the muscle lasts progressively longer in progressively more distal segments; hence, it may play an important role in the normal propagation of primary peristalsis.⁴

The pattern of activation of the inhibitory and excitatory vagal pathways, the regional gradients of inhibitory and excitatory myenteric nerves, and the intrinsic properties of the smooth muscle all determine the latency between swallow and contractions and the velocity of peristalsis. The esophageal peristaltic contractions themselves are a blend of non-cholinergic and cholinergic components. As a consequence, cholinergic antagonists, such as atropine, increase the latency and decrease the amplitude of contraction in the proximal, but not the distal parts of the esophagus. In contrast, antagonists of nitric oxide synthase reduce the latency mainly in the distal segments and lead to simultaneous contractions.

Any condition in the gastrointestinal tract which impairs neural inhibitory activity will probably result in a disorganized motor behavior. In the esophagus, the classical example of degenerative loss of neurons and impairment of inhibitory activity is achalasia of the LES. In 1970, Christensen⁸ suggested that a system of local inhibitory innervation was crucial to the understanding of the pathogenesis of diffuse esophageal spasm and achalasia. Evidence of inhibitory dysfunction associated with abnormal peristalsis and/or incomplete LES relaxation has been found both in animal experiments^{9,10} and in patients with achalasia.¹¹⁻¹⁴ Since then, many investigators proposed that the spectrum of primary esophageal motility disorders may be due to different degrees of inhibitory dysfunction.^{8,15-18}

Given the fact that deglutitive inhibition and latency intervals are crucial in determining propagation of contractile activity in the esophagus, new metrics focused on defining latency, and contractile velocity have been devised using EPT. The clear description of the timing of important events with EPT, such as the onset of swallowing and the contractile deceleration point, have allowed a more uniform description of latency and velocity. These new measurements have been integrated with other measurements focused on the integrity and vigor of contraction to determine phenotypes of rapid propagation that may be both clinically relevant and physiologically distinct.

ESOPHAGEAL PRESSURE TOPOGRAPHY

Anatomy and landmarks

Fig. 1 depicts the typical pressure topography of both sphincters and the intervening esophagus during a

normal swallow. Clouse¹⁹ originally described three types of pressure troughs in the topography of peristalsis, labeled P (proximal), M (middle), and D (distal). Although the clinical relevance and neuromuscular control of these segments remains unclear, swallows may also exhibit exaggerated troughs with defects in the 20 mmHg isobaric contour. Defects within the proximal trough had previously been labeled a transition zone defect based on the hypothesis that this area represented a transition in the neuromuscular control of the esophagus from extrinsically controlled striated muscle to intrinsically dominated smooth muscle. Defects in this particular location, which are >2 cm using a 20 mmHg isobaric contour can be associated with impaired bolus transit and proximal stasis.^{20–22} In contrast, defects associated with the middle and distal pressure troughs are more in line with what would be defined as ineffective esophageal motility, given the proximity of the middle and distal trough with the 3–8 cm domain above the LES utilized in defining this entity.

In addition to the segmental architecture displayed by the Clouse Plots, another important landmark becomes apparent, which has important implications in the context of assessing propagation. The contractile

deceleration point (CDP) is defined as the point where the most abrupt deceleration in velocity occurs within the distal esophagus.²³ This landmark defines a transition from esophageal peristaltic clearance to emptying of the phrenic ampulla on fluoroscopy, where the mechanism of emptying is dominated by compartmentalized pressurization, re-elongation and recoil of the phrenoesophageal ligament rather than peristaltic propagation.²³ The CDP location is determined by defining the intersection point between two tangent lines of the 30 mmHg isobaric contour: one extending distally from the transition zone and the other extending proximal from the EGJ when it reestablishes its normal postdeglutitive position (Fig. 1). The distance of the CDP above the proximal margin of the EGJ typically ranges from 1.5 to 2 cm and thus, the previous landmarks to assess peristalsis using 3 and 8 cm above the LES, were in fact a reasonable estimate of peristaltic function.

Assessing propagation using esophageal pressure topography metrics

The assessment of peristaltic integrity should always be the first step in the evaluation of peristaltic function

Table 1 Esophageal pressure topography metrics utilized in assessing propagation

Measures focused on anatomy and landmarks must be defined before qualifiers can be measured

Peristaltic integrity

Is measured using the 20 mmHg isobaric contour to failed swallow: integrity of the 20 mmHg isobaric contour distal to the proximal pressure trough (P) measures <3 cm in length

Peristaltic breaks: (cm) gaps in the 20 mmHg isobaric contour of the peristaltic contraction between the UES and EGJ, measured in axial length
Small (2–5 cm)
Large (>5 cm)

Contractile deceleration point

(time, location)

Is not measured in a failed swallow or a swallow with a large >5 cm defect in the distal esophagus (D) as it is localized within 5 cm of the EGJ

The inflection point along the 30 mmHg isobaric contour where propagation velocity slows demarcating the tubular esophagus from the phrenic ampulla

This landmark is important in defining distal latency and contractile front velocity

Qualifiers of contractile vigor and propagation should not be measured in failed or swallows with >5 cm breaks in the distal pressure trough

Contractile front velocity

CFV (cm s⁻¹)

Slope of the tangent approximating the 30 mmHg isobaric contour between transition zone (P) and the CDP
Abnormal is >9 cm s⁻¹

Distal latency

DL (s)

Interval between UES relaxation and the CDP
Abnormal is <4.5 s

Distal contractile integral

DCI (mmHg-s-cm)

Uses a space-time box to measure amplitude × duration × length (mmHg s cm) of the distal esophageal contraction >20 mmHg from proximal (P) to distal (D) pressure troughs
>5000 is abnormal
>8000 is not found in control populations

as the integrity of the contraction will determine whether other measurements are feasible or worthwhile (Table 1). The integrity of the contraction using a 20 mmHg isobaric contour associated with each swallow describes how completely that contraction spans from the upper sphincter to the EGJ, irrespective of the vigor or velocity of the contraction. Qualifying measures of Distal Latency (DL) and Contractile Front Velocity (CFV) can only be measured accurately when there is sufficient contractile integrity to allow proper landmark identification and measurement.

Defects or breaks in peristaltic activity can be severe to the point where no propagating contractile activity is present or only a short segment of contraction defined by a 20 mmHg isobaric contour <3 cm is noted.^{24,25} These swallows are defined as failed and therefore, DL or CFV should not be measured. Defects are further defined based on size of the breaks [large >5 cm but not failed, small 2–5 cm].²⁵ Large defects noted in the distal esophagus will potentially conceal the CDP and thus, DL and CFV may be difficult to interpret. These swallows are more akin to swallows labeled as ineffective esophageal motility (IEM) as they will have peristaltic amplitudes below 30 mmHg in a pressure sensor placed 3–8 cm above the EGJ. Therefore, one would define these swallows based on the defect in integrity as a weak swallow, and a determination of abnormal propagation will not be possible.

Small breaks in the peristaltic wavefront may not obscure measurement of the CDP, and thus DL and CFV can be measured when these defects are not localized at the middle or distal trough. Defects occurring at the proximal trough or transition zone should not complicate the determination of the CDP and will not alter the accuracy of measuring DL and CFV.²⁶

Velocity The measurement of peristaltic velocity is the primary criterion for diagnosing spasm using conventional manometry based on the concept that a velocity >7.5–8 cm s⁻¹ is synonymous with a simultaneous contraction.²⁷ However, esophageal pressure topography has revealed that velocity along the contractile wavefront is dependent on contractile morphology and regional changes in distal propagation. This is most notable in the description of the CDP, which describes a clear demarcation of two distinct areas of functional activity focused on changes in velocity along the propagating wavefront. Propagation of the contractile wavefront beyond the CDP is not peristaltic as it represents emptying of the phrenic ampulla. Therefore, a more accurate assessment of peristaltic velocity is made by taking the best-fit tangent between the transition zone and CDP. This is in contrast to the arbitrary

utilization of 3 and 8 cm above the EGJ, where the assessment of peristaltic velocity may extend into the phrenic ampulla.

The CFV is calculated by taking the best-fit tangent between the transition zone and CDP (Fig. 1). In instances of increased intrabolus pressure, trapped between the distal esophageal contraction and the EGJ, the CFV should be determined at an isobaric contour pressure exceeding EGJ pressure so as not to mistake esophageal pressurization for a simultaneous contraction.²⁸ The upper limit of normal for the CFV is >9 cm s⁻¹ based on 95th percentile values of data in 75 normal subjects.²³

Latency The DL is a measure that is reflective of peristaltic timing and the period of deglutitive inhibition rather than the late phase of esophageal emptying. The measurement is made by taking the time from the start of upper esophageal sphincter (UES) relaxation to the CDP and represents a means for quantifying the latency of the distal contraction as a surrogate for inhibitory ganglionic integrity²⁹ (Fig. 1). A computer simulation using normalized measurements of esophageal length determined that the median DL was 6.0 s (95% CI 4.8–7.6 s).³⁰ A manual analysis of the same data found that the median time for propagation from the start of UES relaxation to the CDP was 6.2 s with a minimal value observed of 4.6 s in the control group. Given these findings, a cut-off of 4.5 s was established as the lower limit of normal for the DL. This threshold is also similar to the values previously described by Behar and Biancani²⁹ with a small shift to account for the difference in landmarks for the beginning of the swallow. Although DL can be measured with conventional manometry, it is difficult to standardize because of gaps in pressure sensor spacing and poor identification of the segmental boundaries of the contraction.

Contractile vigor Although contractile vigor is an important measure of overall peristaltic function, it does not have a significant impact on defining the timing and coordination of the contractile wavefront. That being said, abnormalities of contractile vigor may represent an imbalance in the neurologic input of the smooth muscle esophagus and thus, could potentially define relevant pathology. The EPT metric devised to characterize the vigor of the distal esophageal contraction is the Distal Contractile Integral (DCI), measured for the segment spanning from the proximal to distal pressure troughs.³¹ To exclude the effects of intrabolus pressure in the DCI computation, the first 20 mmHg is ignored.³¹ The upper limit of normal

defined by the 95th percentile in a normal population is 5000 mmHg-s-cm.³¹

The conventional criteria of distal esophageal spasm utilized a cut-off threshold value of 30 mmHg to distinguish contractile activity from non-contractile pressure events in the esophageal body.²⁷ Similarly, EPT does require a minimum contractile activity that is defined by assessing the peristaltic integrity using the 20 mmHg isobaric contour. The DCI was devised primarily to identify swallows of excessive contractile vigor and thus, there is no lower limit for DCI to use as a criterion for determining whether a swallow has sufficient vigor to be potentially classified as spastic. The fall back has been to utilize the peristaltic integrity as an inclusion criterion and a diagnosis of spasm cannot be made in the presence of failed swallows, swallows with large breaks in the distal trough or when pan-esophageal pressurization is present.

Pressurization preclude measuring DL and CFV as the accuracy and relevance of these measures remains unclear in these swallow types.

In contrast to defining threshold contractile levels to define inclusion criteria for disorders of rapid propagation, DCI measurements above normal values may have clinical relevance. This is most apparent in the instances where the DCI value is >8000 mmHg-s-cm where contractions are typically associated with repetitive contractions that may extend beyond the timing of the normal deglutitive swallow window.²⁸ These swallows may represent a disorder of altered neurogenic input as the termination of the contraction is abnormal. These patterns of hypercontractility can be seen in patients with and without abnormal propagation of the contractile wavefront and the clinical relevance of these contractile patterns will be covered in another review in this supplement.

PHENOTYPES OF RAPID PROPAGATION

The classification of esophageal motor disorders associated with rapid peristaltic propagation has been refined to include a measure focused on deglutitive inhibition in addition to the standard definition focused on peristaltic velocity. The diagnosis of distal esophageal spasm using conventional criteria utilized a peristaltic velocity threshold of >7.5–8.0 cm s⁻¹ as criteria for spasm with the caveat that the contractile activity was >30 mmHg at the level of 3 and 8 cm above the EGJ.²⁷ However, this definition of DES identifies a very heterogeneous population as evidenced on an assessment of bolus transit in 71 such patients with combined manometry and impedance.³²

Thus, new criteria utilizing EPT metrics focused on CFV and DL have been proposed to improve the categorization of disorders of rapid propagation.

Although quantifying DL is not unique to EPT,^{33,34} the technique simplifies and potentially standardizes this measurement. The EPT provides the detail required to define the segmental architecture of peristalsis necessary to differentiate regional variations in contraction velocity. In addition, it allows one to define the onset of the swallow and the point where esophageal contraction shifts from peristalsis to ampullary emptying. These landmarks are crucial for accurate measurement of the CFV and DL.

A recent study applied carefully standardized metrics for CFV and DL to a large series (1070 consecutive studies) of clinical high resolution EPT studies in an attempt to refine the diagnosis of DES.²⁶ The results defined three distinct subtypes of rapid propagation: (i) rapid premature contraction, (ii) premature contraction and (iii) rapid contraction with normal latency (Fig. 2). Only 2% subjects ($n = 24$) in that series were defined as having premature contractions [reduced DL]. This categorization is important because it is never encountered in asymptomatic control populations and these swallows will also have impaired deglutitive inhibition during multiple rapid swallows. These patients are classified as having Distal Esophageal Spasm in the Chicago Classification if there is evidence of normal EGJ relaxation (Mean Integrated Relaxation Pressure <15 mmHg). Only six patients (0.5%) in this series were classified as true DES based on the criteria of reduced DL and a rapid CFV in 20% or more swallows highlighting the fact that this disorder is extremely rare. Patients with reduced DL and rapid CFV in the context of abnormal EGJ relaxation (Mean Integrated Relaxation Pressure <15 mmHg) are classified as having Type III achalasia.

Rapid contractions with normal latency is a much more common entity compared to premature contractions.²⁶ In the same series of 1070 patients, 67 patients (6%) fulfilled criteria for rapid contraction with normal latency in 20% or more swallows using the Chicago Classification definition. The majority of these patients were ultimately classified as having either weak peristalsis (61%) with a proximal defect or otherwise normal/borderline normal peristalsis with normal transit mechanics. The clinical implication of rapid contraction with normal latency remains unclear and probably rests within the confines of a normal variant or weak peristalsis. Interesting physiologic studies using low doses of atropine reveal that rapid contractions can be shifted to the right suggesting a potential neural cholinergic issue at the transition zone and

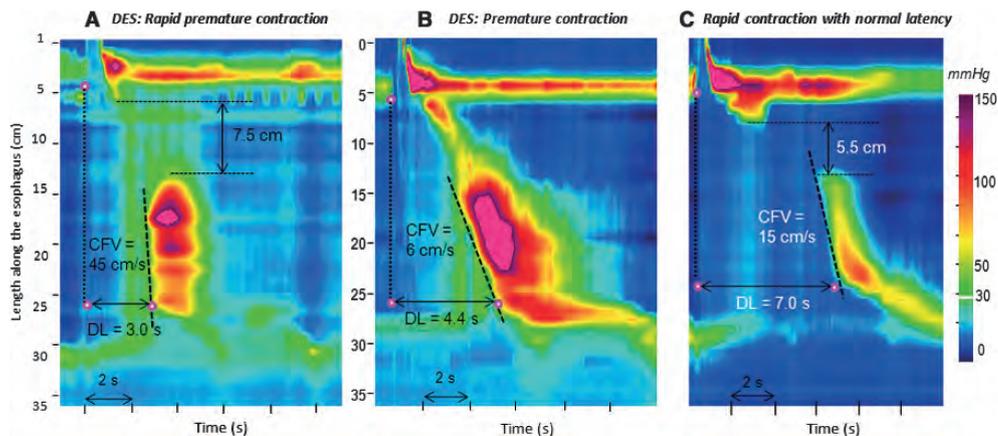


Figure 2 Phenotypes of rapid propagation. Disorders of propagation are defined by two criteria: (i) Premature contraction characterized by a reduced Distal Latency (DL, measured from onset of swallow to the Contractile Deceleration Point <4.5 s) and (ii) Rapid contraction defined by a rapid Contractile Front Velocity (CFV, measured from the proximal trough to the Contractile Deceleration Point to be $>9 \text{ cm s}^{-1}$). Classification of Distal Esophageal Spasm (DES) requires that the contraction be premature with (Panel A) or without (Panel B) rapid contraction. Swallows associated with premature contraction will have impaired bolus transit secondary to entrapment of the bolus within the esophageal body and thus, represents a manometric correlate of the ‘corkscrew’ or ‘rosary bead’ esophagus. Swallows which meet criteria for Rapid Contraction with Normal Latency (Panel C) are differentiated from Distal Esophageal Spasm to highlight the overlap with normal and weak peristalsis. This swallow is associated with a large break in the proximal pressure trough which may obscure the measurement by shifting the starting point for the Contractile Front Velocity determination to the right. The bolus transit abnormality in this example is a manifestation of proximal escape through the wavefront and not entrapment which is seen with Distal Esophageal Spasm.

future studies should focus on assessing the effects of atropine and nitric oxide inhibitors on these subtypes of rapid propagation.

CONCLUSION

Incorporating the measurement of DL into the diagnostic algorithm for assessing esophageal motor disorders has helped define distinct pathophysiologic phenotypes of rapid propagation.²⁶ Disorders of rapid propagation are now defined into categories based on this measurement using the Chicago Classification system. Distal Esophageal Spasm and Type III achalasia are associated with premature contractions characterized by functionally impaired inhibition in the distal esophagus [reduced DL]. In contrast, rapid contraction with normal latency is a separate diagnosis highlighting preserved deglutitive inhibition and the overlap with normal and weak peristalsis. Although this classification is based on definitions extrapolated from prior physiologic investigations and the assessment of simulations in normal asymptomatic controls, the clinical relevance of this classification scheme needs to be tested in long-term natural history studies and outcome trials. We theorize that this distinction may have clinical

relevance in directing therapy in that patients with reduced latency should respond better to agents that target smooth muscle relaxation (calcium channel blockers, nitrates, phosphodiesterase type five inhibitors). On the contrary, patients with rapid contraction and normal latency would probably do poorly with treatment focused on inducing smooth muscle relaxation and would be more suitable with a management approach similar to weak peristalsis or functional dysphagia. Further work will also require a focus on defining physiologic responses to various pharmacologic interventions and provocative swallows to determine the appropriate threshold levels and targets for treatment.

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CONFLICT OF INTEREST

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REVIEW ARTICLE

Achalasia and esophago-gastric junction outflow obstruction: focus on the subtypes

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Abstract

Background *The choice between pneumatic dilation and surgical myotomy is mainly determined by the preference and expertise of the treating physician. Ideally, however, treatment should be personalized to provide the optimal clinical outcome. The introduction of high resolution manometry has not only improved the specificity to diagnose achalasia, but also identified three different manometric subclasses.*

Purpose *To review, the data suggesting differences in clinical response to treatment depending on the manometric profile.*

Keywords *achalasia, laparoscopic Heller myotomy, pneumodilation.*

INTRODUCTION

Achalasia is a relatively rare esophageal motility disorder characterized by an impaired lower esophageal sphincter (LES) relaxation and the absence of esophageal peristalsis, resulting in a functional outflow obstruction at the esophago-gastric junction (EGJ)¹. Although the pathogenesis of achalasia remains unknown (and no definitive therapy is therefore available), the medical community learnt nearly hundred

years ago how to palliate dysphagia in achalasia patients by lowering the LES pressure by cutting the cardia muscular coat² (myotomy) or disrupting its fibers with forceful endoscopic dilations³, or, more recently, by paralyzing them with botulinum toxin⁴. This last solution has been shown to have only a temporary effect and is now considered only for high-risk patients or as a bridge to more definitive therapies.

PNEUMODILATION OR LAPAROSCOPIC HELLER MYOTOMY?

The choice between pneumatic dilations and surgery has been swinging like a pendulum for many years: at the very beginning, dilations were burdened by an excessive risk of perforations and myotomy was generally preferred. With the advent of low-compliance, non-expandable balloons of increasing diameters in the 1980s, the risk of perforation was substantially reduced and pneumatic dilation (PD) became the primary form of therapy for achalasia, whereas surgery was relegated to an ancillary role for treating PD failures. Thanks to the introduction of minimally invasive surgery in the early 1990s, the last 20 years have witnessed a gradual shift in the treatment algorithm for this disease and nowadays, laparoscopic Heller myotomy (LHM) has been recommended as the first choice for achalasia treatment⁵. In the 'real world', however, the physician's expertise, the patient's personal preference and the local availability of an experienced surgeon or endoscopist have been the main determinants orienting the choice of therapy⁶. A large randomized trial recently demonstrated that LHM and a series of PDs achieve the same results in treating dysphagia in achalasia

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patients: both therapies were effective in nearly 90% of patients with a medium follow-up of 3 years⁷. This remarkable result raises the question of why both treatments sometimes fail.

PROGNOSTIC FACTORS

In general, failures – especially early after treatment – have been interpreted as the outcome of faulty technique in performing the LHM (short or incomplete myotomy, mainly in the distal part of the LES)⁸ or PD (inadequate dilation due to insufficient pressure or small balloon diameter, or short dilation time, or dislocation of the balloon). It is certainly peculiar, however, that after a careful standardization of both treatments (PD and LHM), and even in the hands of experienced surgeons and endoscopists, the failure rate is much the same, giving the impression that this 10% of patients represent a ‘minority’ of achalasia patients in whom whatever therapy is attempted is likely to fail.

Few predictors of the outcome of therapy for achalasia have been described: the presence of a large, decompensated sigmoid-shaped mega-esophagus is generally accepted to be a negative prognostic factor for both PD and LHM. Young age (<40 years), a high posttreatment LES pressure (>10 mmHg) and incomplete obliteration of the balloon’s waist during PD are negative prognostic factors for PD^{9,10}. Daily chest pain, an esophagus <4 cm wide before treatment, and stasis on the barium esophagogram after treatment were recently identified as other negative prognostic factors for both treatments⁷. An LES resting pressure >35 mm Hg is reportedly a positive prognostic factor for LHM¹⁰. Be that as it may, the reasons for any treatment failures remain obscure in most cases.

ESOPHAGEAL MANOMETRY VS HIGH RESOLUTION MANOMETRY

Ideally, we should aim to develop criteria enabling customized patient care, such that the most efficient therapy is recommended to each patient. Identifying positive and negative prognostic factors based on clinical features is therefore highly relevant to clinical patient management. Until recently, manometry was only used to diagnose achalasia and monitor the efficacy of treatment to reduce the LES pressure. Pull-through manometry and, later on, sleeve manometry have both proven very useful for these purposes. Two major improvements have been accomplished, however, with the introduction of high resolution manometry combined with pressure topography plotting: (i)

the sensitivity of the diagnosis of achalasia has significantly improved; and (ii) manometric subtypes have been identified that are associated with different outcomes of treatment.

As discussed in detail by Bansai and Kahrilas¹¹, a catheter containing 36 solid sensors placed 1 cm apart is easy to position, and eliminates any difficulties with interpreting tracings due to an erroneous positioning of the manometric catheter. The use of the high resolution manometry (HRM) catheter eliminated the pitfall of erroneously interpreting as a normal relaxation, the upward movement of the LES relative to the pressure or sleeve sensor and the consequent relocation in the stomach of the normal or sleeve catheters. More detailed information on the esophageal and LES pressure profiles is provided too, significantly increasing the diagnostic yield. In particular, pressurization of the esophagus can be better distinguished from non-propulsive high-amplitude contractions, whereas pseudorelaxation of the LES during swallowing due to esophageal shortening (up to 9 cm) is no longer an issue.

More detailed manometric recording and data representation in pressure topography plots have given rise to a new algorithm for classifying esophageal motility disorders, including achalasia. Although the diagnosis of achalasia focuses primarily on impaired LES relaxation and subsequent outflow obstruction, abnormalities in contractile and pressurization patterns in the esophageal body determine three different subtypes of achalasia, depending on any presence of complete failure of peristalsis or spastic contractions¹¹. Each swallow is characterized as normal (intact isobaric contour line (pressure front velocity – PFV $\leq 8 \text{ cm s}^{-1}$), failed (complete failure of contraction), hypotensive (>2 cm break in the 30 mm Hg isobaric contour line), rapidly conducted (PFV $\geq 8 \text{ cm s}^{-1}$) spastic contractions, or panesophageal pressurization with simultaneous esophageal pressurization extending from the upper esophageal sphincter (UES) to the EGJ. Using these definitions, patients can be classified as: type I, achalasia with minimal or no esophageal pressurization in 8 of 10 swallows; type II, achalasia with esophageal compression (at least); or type III, achalasia with spasm (Figs 1–3). Most importantly, the authors also suggested a correlation between the manometric subtype and the final outcome of treatment.

ACHALASIA SUBTYPES AND SUCCESS OF TREATMENT

In their series of 99 achalasia patients, Pandolfino *et al.*¹² classified 21 patients as type I, 49 as type II, and

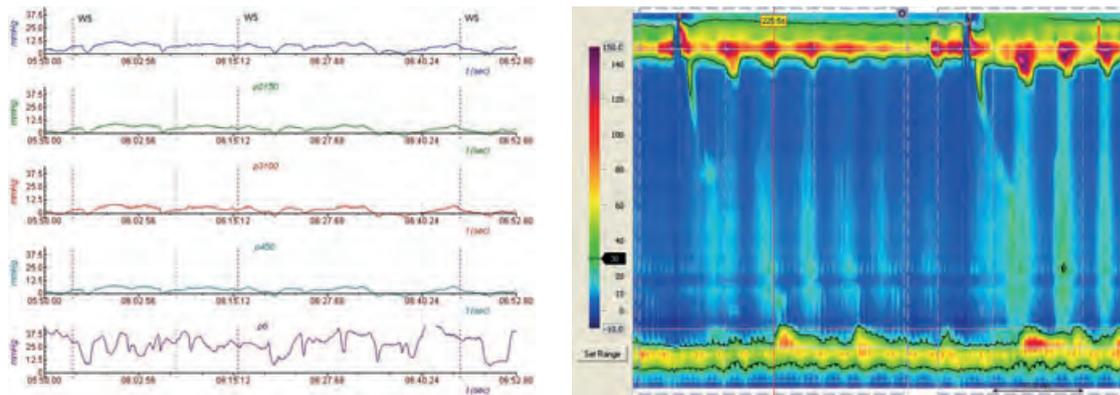


Figure 1 Type I Classic achalasia (A) analogic trace and (B) color pressure topography. No distal esophageal pressurization is evident and all the contractions elicited by liquid swallows have an amplitude >30 mm Hg.

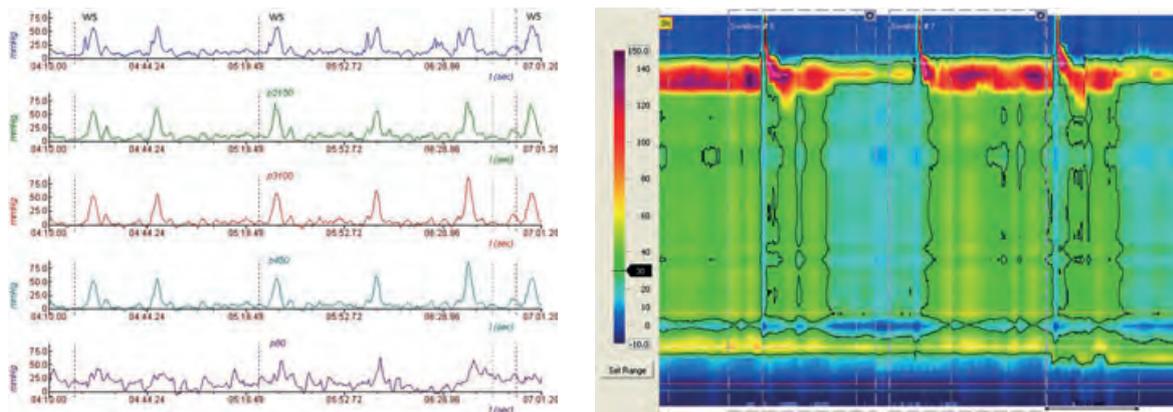


Figure 2 Type II achalasia (A) analogic trace and (B) color pressure topography. Simultaneous isobaric esophageal pressurization is evident at HRM and all the contractions elicited by liquid swallows have an amplitude \leq 30 mmHg, with normal duration.

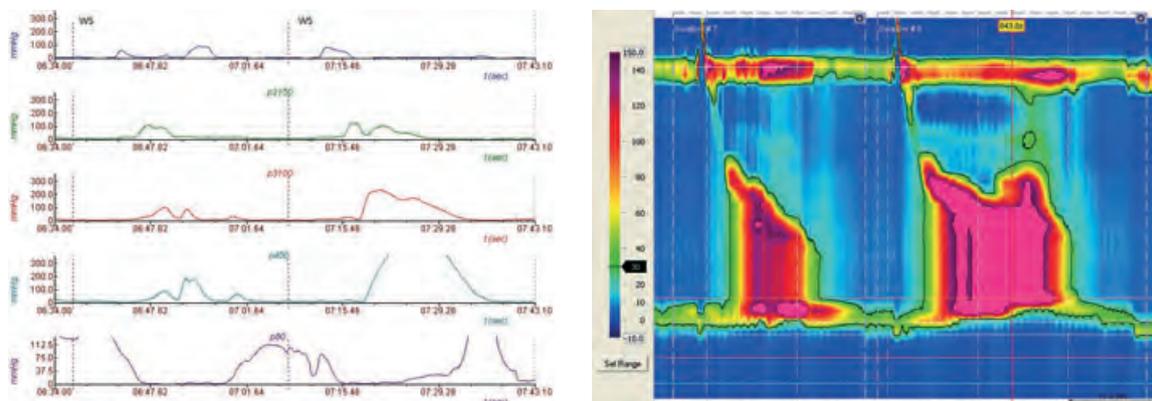


Figure 3 Type III achalasia (A) analogic trace and (B) color pressure topography. High-resolution manometric picture of rapidly propagating pressurization with spastic contractions. The high amplitude contractions of the distal esophageal body is represented by the red high-pressure area of the esophageal body contraction. (B) Conventional manometry of long-lasting, high-pressure spastic esophageal contraction.

29 as type III; follow-up information in sufficient detail and of sufficient duration (at least a year) was available for 83 of these patients. Fourteen patients were given

botox injections, 43 were treated with PD, and 26 underwent LHM. From a clinical point of view, type I patients were more likely to have esophageal dilation,

Table 1 High resolution manometry achalasia subtyping and outcome of treatments

Author	Subtype	No. patients (%)	Success rate	
			PD	LHM
Pandolfino	I	21 (21.2)	56*	
	II	49 (49.5)	96*	
	III	29 (29.3)	29*	
Salvador (LHM)	I	96 (39)	84.6	
	II	127 (51.6)	95.3	
	III	23 (9.4)	69.3	
Pratap (PD)	I	24 (47.1)	63	
	II	24 (47.1)	90	
	III	3 (5.8)	33.3	
Rohof (PD & LHM)				
	I	44 (25)	85.7	81
	II	114 (64.7)	100	95
	III	18 (10.2)	40	86

LHM, laparoscopic heller myotomy; PD, pneumatic dilatation.

*Success after last intervention (Botulinum toxin injection, Pneumatic Dilatation or Laparoscopic Heller Myotomy were performed as first intervention; a second dilatation with larger balloon or Laparoscopic myotomy were performed as last intervention).

whereas type II and III patients had chest pain significantly more often. The success of treatment was strongly influenced by the achalasia subtype, irrespective of the type of therapy involved. Achalasia subtype II was much more likely, and type III much less likely to respond to treatment than type I (Table 1). Patients with type II did respond excellently, with a success rate of 96%, as opposed to 56% and 29% for types I and III, respectively. In this study, success was defined as a documented improvement recorded at one or more postintervention clinical visits, such that no further intervention was recommended for at least 12 months. Although patients with type I achalasia seemed to respond best to LHM, the number of patients involved was rather small and larger studies are needed to confirm this finding. It became clear from subsequent studies, however, that the success of therapy is indeed determined by the achalasia subtype. Although largely conventional (sleeve) manometry rather than high resolution manometry was used in these studies, similar patterns can be distinguished with this technique allowing reliable sub-classification. In a large series of patients treated with LHM, Salvador *et al.*¹³ studied 249 consecutive patients (with a median follow-up of 31 months): 39% of patients were classified as having achalasia type I, 51.6% as type II and 9.4% as type III (Table 1). Patients were considered treatment failures if their postoperative

symptom score was >7. At multivariate analysis, the manometric pattern was confirmed as an independent predictor of success: type II patients responded best to treatment (95.3% success rate), and patients with type III had the lowest response rate (69.6%). A smaller study reported on the short-term results (after a mean follow-up of 6 months) in 45 achalasia patients treated with PD¹⁴. As in the previous studies, patients with type II had a better clinical response (90%) than types I (63%) or III (33%) (Table 1). Finally, when the manometric tracings of the achalasia patients included in the European achalasia trial were classified according to the criteria proposed by Pandolfino *et al.*, type I achalasia was identified in 44 patients (25%), type II in 114 (65%), and type III in 18 (10%)¹⁵. Of these 175 patients, 84 were randomized to PD and 91 to LHM. After 2 years of follow-up, the success rates were significantly higher for type II cases (96%) than for type I (81%) and type III (66%) patients, irrespective of the type of treatment¹⁵ (Table 1). The response rate was particularly low in type III patients who had PD ($n = 10$, 40% success rate), but otherwise largely comparable for PD and LHM in types I and II.

CONCLUSIONS

On the basis of the information reported to date, the evidence clearly confirms that the subtype of achalasia is an independent predictor of success, with type III having the worst outcome after therapy. To what extent the subtypes represent different phenotypes or simply reflect different stages of the disease is hard to say. Recent detailed analyses of HRM tracings, combined with impedance and ultrasound images, seem to suggest that type III and type I achalasia, respectively, represent the feature of a compensated and decompensated esophagus to outflow obstructions caused by a dysfunctional LES¹⁶. The pressurization pattern typical of type II achalasia, on the other hand, stems from another, novel motor response of the esophagus involving longitudinal muscle contractions of the distal esophagus.

Be that as it may, it seems fair to conclude that type III achalasia, characterized by well-defined, lumen-obliterating spastic contractions in the distal esophagus, responds the least to therapy. In this subgroup of achalasia patients, reducing the LES pressure may not suffice to control the symptoms, especially as the segment affected by the spastic motility extends well above the LES. Chest pain, a prominent symptom in type III achalasia patients (probably associated with spastic contractions), is especially difficult to treat, explaining the lower success rates in these patients.

The response to therapy in type II is rather better than that in type I, but in the European Achalasia Trial, at least there were apparently no major differences in the success rate for these subtypes between PD and LHM. Judging from the available data therefore, classifying

achalasia according to its subtypes helps us inform patients with type III better about their presumably less favorable outcome, though we are not yet at a stage where the choice of treatment (LHM or PD) can be based on HRM findings.

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