

AGA Technical Review on the Clinical Use of Esophageal Manometry

This literature review and the recommendations therein were prepared for the American Gastroenterological Association Clinical Practice Committee. The paper was approved by the Committee on October 2, 2004, and by the AGA Governing Board on November 7, 2004.

The utility of esophageal manometry in clinical practice resides in 3 domains: (1) to accurately define esophageal motor function, (2) to define abnormal motor function, and (3) to delineate a treatment plan based on motor abnormalities. Since the first American Gastroenterological Association technical review on esophageal manometry published 10 years ago,^{1,2} advances have been made within each of these domains. By and large, these advances have not been the result of major technological changes but rather a reflection of improved manometric technique and research. With this in mind, the goal of this second technical review on the clinical use of esophageal manometry is to summarize what has been learned during the past 10 years and discuss how this has modified the clinical management of esophageal disorders. Thus, we performed a literature search for all English-language articles dealing with manometric evaluation of the esophagus from 1994 to 2003. The databases searched included MEDLINE, PreMEDLINE, and PubMed using general terms related to manometric technique (sleeve, topography) and equipment (water perfused, solid state), esophageal symptoms (dysphagia, chest pain, heartburn), esophageal disorders and procedures (gastroesophageal reflux disease, achalasia, diffuse esophageal spasm, nutcracker esophagus, hypertensive LES, nonspecific motor disorders, ineffective esophageal motility, fundoplication, myotomy, dilation), and terms focused on esophageal motor function (upper esophageal sphincter, lower esophageal sphincter, esophageal body, peristalsis). Additional references were identified from references of reviewed manuscripts.

1994–2003: How Has Esophageal Manometry Changed?

Manometry is by nature a highly technical evaluation, more akin to physiologic studies than to endoscopic or radiographic ones. When optimally utilized and providing that physical principles and equipment characteristics are respected, a manometric examination provides an accurate description of esophageal contractile

function. In general, manometric data are only as valid as the methodology used to acquire them.

The frequency content of esophageal contractile waves defines the required characteristics of a manometric recording device. The frequency response required to reproduce esophageal pressure waves with 98% accuracy is 0–4 Hz, while that required for reproducing pharyngeal pressure waves is 0–56 Hz.³ Expressed in terms of maximal recordable $\Delta P/\Delta t$, 300 mm Hg/s will suffice for the mid or distal esophagus versus 4000 mm Hg/s for the pharynx. Because the overall characteristics of the manometric system are only as good as those of the weakest element within that system, high-fidelity recordings require that each element (pressure sensor, transducer, recorder) meet or exceed these response characteristics. Modern computer polygraphs and pressure transducers, essentially unchanged in the past 10 years, have response characteristics greatly exceeding those required for esophageal manometry. Thus, most of the methodological evolution that has occurred during the past 10 years has been in the domains of manometric assembly design and data analysis; each of these will be reviewed.

Manometric Assemblies

The pressure sensor/transducer components of a manometric assembly function as a matched pair and are available in 2 general designs: water-perfused catheters with volume displacement transducers or strain gauge transducers with solid-state circuitry. Major advantages of water-perfused systems are cost and versatility. A major disadvantage is that the equipment is fickle and proper maintenance requires skilled personnel. Illustrative of the versatility possible with perfused manometric assemblies, the past 10 years have witnessed the introduction of multilumen, autoclavable, miniature silicone

Abbreviations used in this paper: DES, diffuse esophageal spasm; EGJ, esophagogastric junction; GERD, gastroesophageal reflux disease; IEM, ineffective esophageal motility; tLESR, transient lower esophageal sphincter relaxation; UES, upper esophageal sphincter.

© 2005 by the American Gastroenterological Association

0016-5085/05/\$30.00

doi:10.1053/j.gastro.2004.11.008

extrusions that can be configured with nearly infinite variety.

Faithful recording of sphincter pressure for extended periods of time or during swallow-related esophageal shortening requires that the pressure sensor maintain a constant position within the high-pressure zone. Sleeve sensors were devised to meet these requirements. However, sleeve sensors were originally made of molded silicone and, before 1994, manometric extrusions were made of polyvinyl chloride. Thus, the sleeve sensor needed to be joined to the end of the polyvinyl extrusion with a complex joint involving metal stents and suture. Although functional, the resultant assembly probably would not meet current requirements for reuse mandated by the need for restoring sterility. On the other hand, the multilumen silicone extrusions currently available (Mui Scientific, Mississauga, Canada; formerly Dentsleeve) can incorporate sleeve sensors directly onto the extrusion, making the resultant assembly both more durable and autoclavable. These catheters have undergone rigorous reuse evaluation and have been deemed safe for reuse by both the Food and Drug Administration (via the 510k mechanism) and EU regulators (CE marked and monitored).

An alternative to perfused manometric systems is a manometric assembly incorporating miniature strain gauge sensors and solid-state electronic components. The microtransducers directly interface with the recorder, and the resultant system has a vastly expanded frequency response suitable for pharyngeal recording. On the negative side, solid-state systems are much more expensive, are less modifiable, are more delicate, and do not yet have the versatility of assembly design permissive of either a sleeve sensor or topographic data presentation (see following text). Improvements in design are currently under way, and it is likely that high-resolution solid-state systems will be available in the near future. One other appeal of solid-state systems is that they are not subject to hydrostatic effects and can be miniaturized, factors that make them more suitable for extended ambulatory studies. Having said that, recent research has shown successful use of a portable water-perfusion pump with a sleeve assembly and the resultant publications have provided substantial insight into the pathogenesis of reflux⁴ and the mechanisms of reflux in patients with and without a hiatus hernia.⁵

Manometric Data Analysis

Given that most manometric recording systems are computer based, the potential exists for automated analysis. Automated analysis of manometric tracings is an appealing concept because it could lead to standard-

ization of what has otherwise been a highly operator-dependent evaluation. However, the pitfalls of interpreting esophageal manometric tracings are plentiful. For example, pressure thresholds established to distinguish contractions from miscellaneous artifacts may ignore hypotensive peristaltic contractions below that threshold. Similarly, the ability of automated analysis to accurately characterize the adequacy of lower esophageal sphincter (LES) relaxation or to differentiate isobaric common cavities from spastic contractions has not been adequately validated. These subtle distinctions can be absolutely crucial in establishing an accurate diagnosis. Thus, although currently available programs may be useful adjuncts in the interpretation of (normal) manometric recordings, automated analysis has not yet matured to a degree that it can replace manual inspection by an experienced clinician. Guidelines for performance of esophageal manometry and standardized reporting are crucial to decrease the degree of subjective interpretation between clinicians. Although not covered in this review, detailed methods regarding these issues were recently published by members of the American Motility Society and the European Society of Neurogastroenterology and Motility Working Group on Esophageal Manometry.⁶

An offshoot of the introduction of multilumen miniature extrusions has been the application of topographic data presentation to manometric recordings. Topographic analysis is a method of axial data interpolation derived from computerized plotting of data from multiple, closely spaced recording sites.⁷ The interpolated pressure information is plotted as either a 3-dimensional surface plot or a 2-dimensional contour plot in which pressure amplitude is represented by concentric rings or color gradients with an appropriate scale (Figure 1). The advantage of this presentation is that it provides a complete, dynamic representation of peristalsis at every axial position along the esophagus, as opposed to the fragmented data presented in conventional manometric tracings. However, even though this technique has provided significant insight into the physiology of peristalsis and has the potential to redefine the way we evaluate sphincter relaxation, it is debatable as to whether or not it has yet demonstrated any clear advantage over conventional manometry in clinical practice.⁸

Intraluminal Impedance Monitoring

Although manometric apparatus has not changed significantly in the past 10 years, there has been significant interest in combining manometry with a newly evolving technology, intraluminal impedance monitoring. Impedance monitoring works by quantifying the impedance between pairs of metal

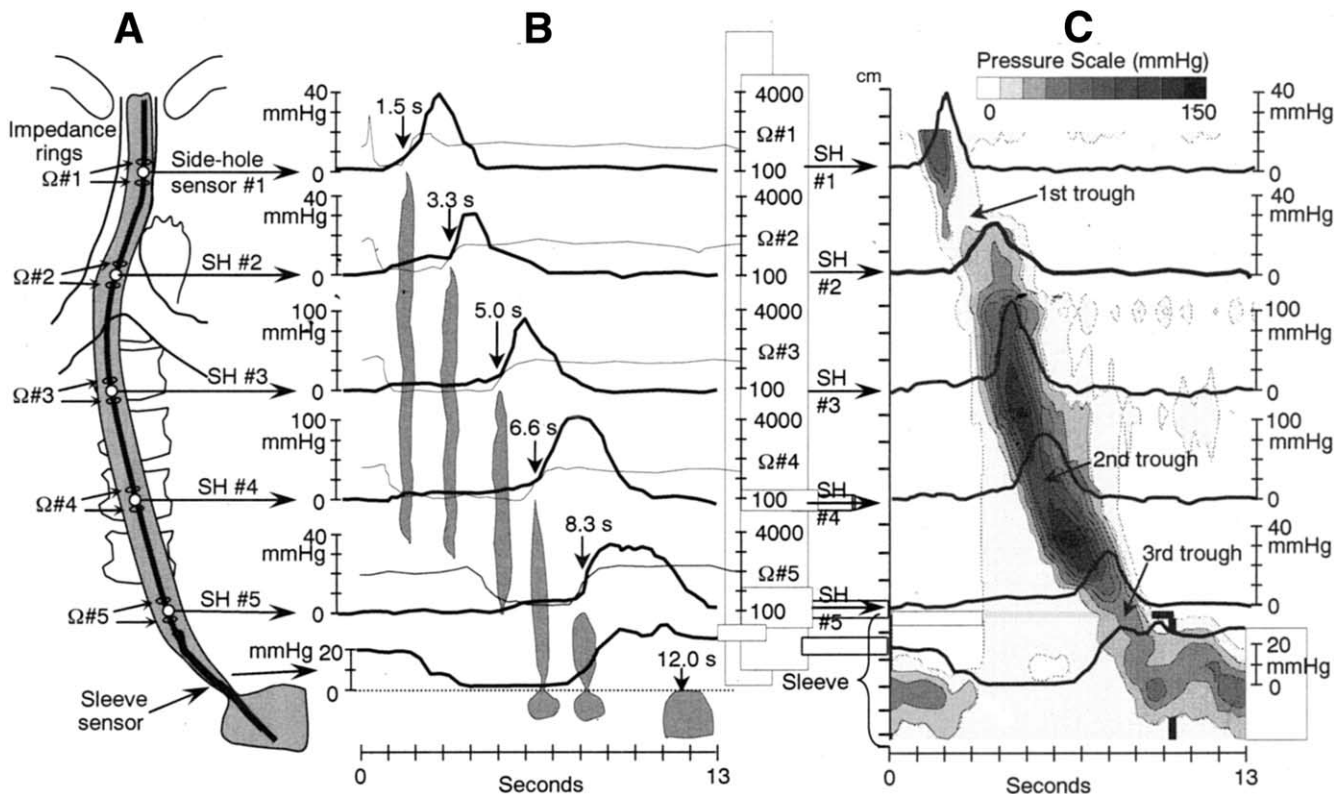


Figure 1. Representative physiologic data, modified to illustrate the relationship between videofluoroscopic, manometric, impedance, and topographic representations of esophageal peristalsis. (A) Schematic drawing of placement of a combined manometry/intraluminal impedance monitoring system with 5 manometric side holes (SH) spaced 4 cm apart and a 6-cm sleeve sensor placed just distal to the last manometric port. The impedance rings (Ω) are also spaced 4 cm apart with the rings straddling the manometric ports. The arrows to B point to the corresponding data tracings obtained from each combined manometry/impedance or sleeve recording site. (B) Concurrent videofluoroscopic, manometric, and multichannel intraluminal impedance recordings of a 5-mL Renografin swallow that was completely cleared by one peristaltic sequence. Representative tracings from the videofluoroscopic sequence overlaid on the combined manometric/impedance tracing show the distribution of the bolus at the times indicated by the vertical arrows. At each recording site, the thick line intersecting the pressure scale (mm Hg) on the left represents the manometric tracing and the fine line intersecting the impedance scale in ohms (Ω) on the right represents the impedance recording tracing. Bolus entry at each combined manometry/impedance recording site is signaled by a subtle increase in pressure (intrabolus pressure) and a >50% decrease in impedance. In this example, the bolus propagates past Ω #4 rapidly indicated by an abrupt reduction in impedance in Ω #2, Ω #3, and Ω #4 at time 1.5 seconds. Luminal closure and hence the tail of the barium bolus is evident at each recording site by the upstroke of the peristaltic contraction and a 50% increase in recorded impedance. Hence, at 5.0 seconds, the peristaltic contraction was beginning at SH#3, corresponding to a 50% increase in impedance and the tail of the barium bolus at the same esophageal locus. Finally, after completion of the peristaltic contraction (time 12.0 seconds), all Renografin was in the stomach. (C) Comparison of conventional manometry obtained with a sleeve assembly as depicted in A and high-fidelity manometry with recording sites at 1-cm intervals displayed topographically as an isocontour plot. The standard manometric recordings are superimposed on the isocontour plot at axial locations corresponding to the equivalent portion of the high-fidelity manometry it represents. In the isocontour plot, deepening shades of gray indicate higher pressures revealing 4 distinct pressure segments separated by 3 pressure troughs. Physiologically the first trough is at the junction between striated and smooth muscle, the second is within the smooth muscle segment, and the third separates the peristaltic segment from the LES. Note that LES relaxation is reliably recorded using either methodology, albeit somewhat differently. From the illustration, it can be seen that the end of LES relaxation measured by the sleeve coincides with the peristaltic contraction contacting the proximal portion of the sleeve. In addition to measuring mean residual pressure, topographic analysis allows for more precise measurement of the transsphincteric pressure gradient. (Isocontour tracing courtesy of Ray Clouse.)

rings dispersed along the combined manometry/impedance assembly. Air, fluid bolus, and the esophageal wall each have unique impedance characteristics, thereby allowing definition of which resides between each pair of electrodes. Defining impedance changes over adjacent pairs of rings defines bolus transit within the esophagus.⁹⁻¹¹ Studies using combined fluoroscopy and impedance have validated the convention

that liquid bolus entry is signaled by a 50% decrease in impedance at the recording site, while bolus exit is signaled by a return to at least 50% of baseline^{12,13} (Figure 1). Currently, impedance monitoring is predominantly used in research as an alternative to fluoroscopy for assessing esophageal transit and emptying. Its role in the clinical evaluation of esophageal motor disorders has not yet been formally assessed.

Advances in Defining Esophageal Motor Function: 1994–2003

Upper Esophageal Sphincter

The muscular elements of the upper esophageal sphincter (UES) are the cricopharyngeus, adjacent esophagus, and adjacent inferior constrictor. The cricopharyngeus inserts bilaterally to the inferior-lateral margins of the cricoid lamina, and the zone of maximal UES pressure is ≈ 1 cm in length at precisely this location.¹⁴ The closed sphincter has a slit-like configuration, with the cricoid lamina anterior and the cricopharyngeus making up the lateral and posterior walls. Thus, it is not surprising that resting UES pressure is markedly asymmetric, with greatest values anteriorly and posteriorly.¹⁵ Because the only insertion of the cricopharyngeus is to the cricoid cartilage, the sphincter and larynx are obliged to move in unison.

Manometric evaluation of UES function is difficult because it is a short, complex anatomic zone that moves briskly during swallowing. Furthermore, measurement of UES pressure is heavily influenced by recording methodology due to both its marked asymmetry and the fact that the measurement, in and of itself, stimulates sphincter contraction. The less movement applied to the recording catheter and the smaller the measuring device, the lower the recorded pressures.² In an extreme demonstration of this, a recent study using a microsleeve sensor in healthy volunteers demonstrated periods of negligible resting pressure in all subjects.¹⁶ Thus, it is not surprising that there is great variability in reported “normal” ranges of UES pressure, and it is currently impossible to define a meaningful normal range.²

UES relaxation during swallowing also poses substantial recording challenges. Relaxation occurs during swallow-associated laryngeal elevation.¹⁴ However, movement of the sphincter and the transnasally positioned catheter are dyssynchronous. The UES may move 2–3 cm proximally during swallowing, whereas the sensor may move only 1 cm.¹⁴ Given the short length of the high-pressure zone, this dissociation simulates relaxation with a focal sensor. Although positioning the recording site at the proximal aspect of the UES to anticipate subsequent movement appears to be a logical solution,¹⁷ movement of both the UES and the catheter may vary among individuals and certainly among various disease conditions, making such an approach unreliable.

Given the methodological challenges detailed above, the utility of UES manometry in clinical practice has been questioned. Illustrative of this, a recent retrospective review of 435 manometric studies with adequate evaluation of the UES and pharynx reported that 80

patients had one or more UES abnormality detected.¹⁸ Among these subjects, 17 patients were known to have or suspected of having an oropharyngeal problem whereas in 58 patients the finding was unexpected. In only 3 subjects with purely UES/pharyngeal abnormalities was there a change in therapy based on the manometric findings; 2 were instructed on dietary modifications and one had swallow therapy initiated. The investigators concluded that routine UES/pharyngeal manometry is of limited clinical utility.

Although routine UES and pharyngeal manometry is of questionable use, studies combining UES and pharyngeal manometry with concurrent fluoroscopy have provided significant insight into the pathogenesis of cricopharyngeal bars and Zenker's diverticula. Using a manometric catheter with 3-cm spacing and exacting videofluoroscopy, Dantas et al questioned the prevailing notion that cricopharyngeal bars were caused by impaired UES relaxation (so-called “cricopharyngeal achalasia”) and instead demonstrated the problem to be of reduced compliance and impaired sphincter opening.¹⁹ More recently, sophisticated analysis of this relationship has been performed using high-resolution, high-fidelity perfused micromanometry to create a topographic mapping of the space-time patterns of hypopharyngeal intrabolus pressure.²⁰ This work beautifully illustrated that the location and magnitude of the intrabolus pressure gradient correlated with the location of maximal UES constriction (Figure 2). Thus, quantifying pressure gradient characteristics and location may serve as a useful clinical indicator for pathologic constriction of the cricopharyngeus muscle and also may define treatment parameters.

Esophageal Body

The body of the esophagus is a 20–22-cm tube, with the muscularis propria comprised of an inner circular layer and an outer longitudinal layer. Primary peristalsis is initiated by swallowing and is evident shortly after the pharyngeal contraction traverses the UES, progressing distally at a velocity of 2–4 cm/s. Secondary peristalsis can be elicited at any esophageal level in response to luminal distention and progresses from the point of stimulation distally. The mechanical effect of peristalsis is a stripping wave that milks the esophagus clean. Progression of the stripping wave corresponds closely with that of the manometric contraction such that the point of the inverted “V” seen fluoroscopically at each esophageal locus coincides with the upstroke of the pressure wave.²¹ However, the recent application of topographic analysis to esophageal peristalsis has clearly demonstrated that progression through the

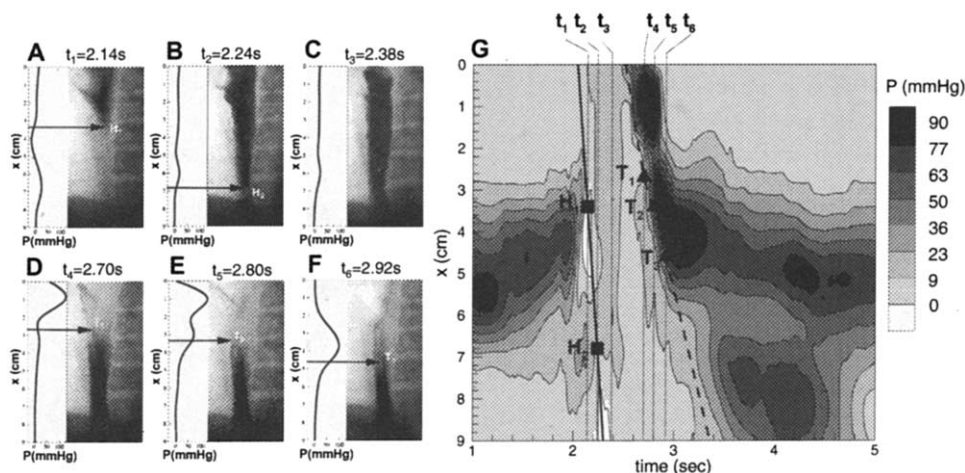


Figure 2. Dynamic representation of UES pressure during a normal swallow derived from concurrent manometry and videofluoroscopy. Radiographic images at selected times from the videofluoroscopic sequence are depicted in A–F. The vertical line in each panel illustrates the pressure value at each axial location along with interpolated values between recording sites. Markers H1–H2 in A and B indicate locations of the bolus head and T1–T3 in D–F the bolus tail, as determined from the videofluoroscopic images at times t1–t6. The isocontour plot (G) combines the data from A–F along with prior, intermediate, and subsequent time points. Pressure magnitudes are indicated by shading. The region of the isocontour plot between the bolus head and tail trajectories is the intrabolus pressure domain during transsphincteric bolus flow. Figure courtesy of A. Pal and J. G. Brasseur. Modified and reprinted with permission from Pal et al.²⁰

esophageal body is not seamless. Rather, it is comprised of a sequence of contractile events occurring in 4 discrete pressure segments (Figure 1). The first segment represents the striated muscle component of the proximal esophagus and extends from the UES to the first pressure trough in the region of the aortic arch. The distal portion of the esophagus is separated into 2 overlapping neuromuscular segments. This observation elegantly explains the double peaked contractions that are found in 10%–15% of healthy subjects. The second pressure peak of the double peak essentially arises from the third topographic segment overlapping with the second segment and initiating its own contraction with a slight delay. The fourth contractile segment encompasses the LES. This segmental configuration was not appreciated by conventional manometry and underscores the strength of topographic analysis of manometric data.^{22–24}

The efficacy of distal esophageal emptying is inversely related to peristaltic amplitude such that emptying becomes progressively impaired with peristaltic amplitudes ≤ 30 mm Hg.²¹ This threshold amplitude was initially determined using simultaneous videofluoroscopy and manometry on a relatively small number of subjects. Recently, multichannel intraluminal impedance has been utilized to assess the efficacy of esophageal emptying as a function of peristaltic amplitude in a much greater number of swallows and subjects.²⁵ Receiver operating characteristic curve analysis of combined manometric/impedance data showed that a 30–mm Hg cutoff for distal esophageal peristaltic amplitude had a sensitivity of 85% and a specificity of 66% for identifying incomplete bolus

transit. With diminishing peristaltic amplitudes, the sensitivity progressively decreased and the specificity progressively increased (Figure 3). This analysis nicely illustrates the complementary nature of manometry and impedance testing and could potentially develop into a valuable clinical tool for the assessment of dysphagia. However, one must be cautious in directly applying the results of Figure 3 to disease or postsurgical conditions. To fully describe the efficacy of esophageal emptying, outflow resistance must also be quantified because this will surely vary with disease or postsurgical conditions.

Conventional manometry can, for the most part, accurately define the peristaltic waveform of the tubular esophagus. However, there are important limitations inherent in the methodology itself. Manometric assemblies are unable to quantify longitudinal muscle contraction or axial movement. Additionally, manometry alone is insufficient to determine whether an intraluminal pressure waveform is the result of an intrabolus pressure or squeeze pressure within a closed lumen. In general, these limitations can be overcome by using complementary methodologies such as fluoroscopy, impedance monitoring, or topographic analysis (Figure 3). Currently, however, these methods are not routinely used in clinical practice.

The Esophagogastric Junction High-Pressure Zone

Physiologically, the esophagogastric junction (EGJ) is a 2- to 4-cm-long asymmetric high-pressure zone attributable to a composite of both the LES and the

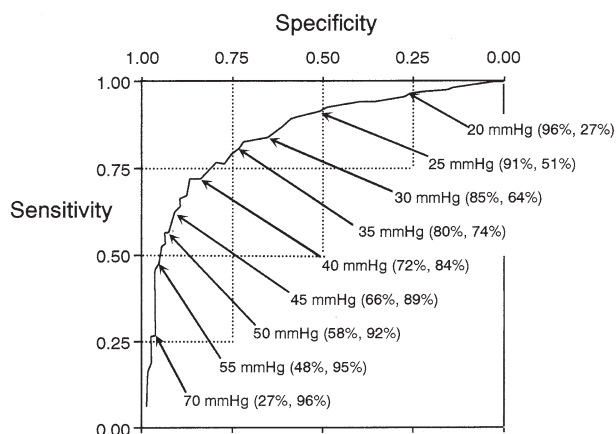


Figure 3. Receiver operating characteristic curves describing the effectiveness of peristaltic contractions in achieving complete esophageal emptying for liquid swallows in subjects with hypotensive peristalsis. These data were generated from combined impedance and manometry studies of 700 swallows in 70 patients with the impedance/manometry segments under analysis positioned 5 and 10 cm above the LES. The curves plot sensitivity against specificity of peristaltic amplitude as a predictor of complete bolus transit. The arrows indicate the position along the receiver operating characteristic curve of several discrete cutoff values of peristaltic amplitudes with the corresponding sensitivity and specificity values (respectively) in parentheses. It is evident from the curve that the peristaltic amplitude that achieves the optimal sensitivity and specificity is between 35 and 40 mm Hg. Modified and reprinted with permission from Tutuian et al.²⁵

surrounding right crus of the diaphragm. Manometric and intraluminal ultrasound studies suggest that axial asymmetry of the pressure profile is attributable to the varying thickness of the circular layer of the muscularis propria, while the radial pressure asymmetry results from asymmetric extrinsic compression by the surrounding diaphragmatic crus.^{26,27} Intrinsic LES tone is a property of the smooth muscle itself and its autonomic innervation.^{28,29} Intra-abdominal pressure, gastric distention, hormones, various foods, and medications alter the intrinsic LES pressure, which typically ranges from 10 to 45 mm Hg.² The contribution of the crural diaphragm to EGJ pressure is evident by the direct correlation between intraluminal EGJ pressure and integrated electromyographic spike activity of the crural diaphragm.³⁰ Mainly as a result of the diaphragmatic contribution, normal EGJ pressure ranges from 15 ± 11 mm Hg at end expiration to 40 ± 13 mm Hg at end inspiration, measured from the same manometric tracings.³¹ Thus, similar to the case of the UES, reported ranges of normal EGJ pressure are highly dependent on methodology. The most meaningful statement that can be made regarding isolated measurement of EGJ pressure is that it is abnormal to have an extremely low value (≤ 5 mm Hg).

The manometric evaluation of LES relaxation is arguably the most important measurement made during clin-

ical esophageal manometry. Relaxation of the LES occurs with swallowing, esophageal distention, and transient LES relaxation (tLESR). However, before the publication of the first technical review, there was a paucity of quantitative data regarding LES relaxation. The deficiency was mostly attributable to the lack of standardized recording methodology and data interpretation. Recognizing this void, recent studies have quantified normal deglutitive EGJ relaxation with techniques suited to study a mobile anatomic zone: either a water-perfused sleeve sensor that spans the sphincteric region or high-resolution manometry with topographic data analysis.

Shi et al used a standardized methodology of sleeve sensor recording and computer-assisted data analysis and concluded that the best single assessment of EGJ relaxation was mean relaxation pressure (Table 1).³² Using the 95th percentile value of controls (12 mm Hg) as the upper limit of normal, this parameter had a sensitivity and positive predictive value of 92% and 88%, respectively, for a diagnosis of achalasia. However, some manometrists measure LES relaxation pressure during end expiration to exclude the contribution of the crural diaphragm.³³ Although this technique is technically a more accurate assessment of the intrinsic sphincter, it is more difficult to standardize the measurement and, hence, a more subjective measurement than the mean LES relaxation pressure. In another study aimed at defining the optimal criteria for incomplete EGJ relaxation, Staiano and Clouse utilized high-resolution manometry with and without topographic analysis.³⁴ They reported that using topographic analysis, a transsphincteric pressure gradient exceeding 5 mm Hg had high sensitivity (94%) and specificity (89%) for achalasia regardless of the presence or absence of peristalsis. Without topographic analysis, the 3-second mean residual EGJ pressure was most discriminative (Table 1).

Although not usually a component of a clinical esophageal manometry study, the use of consistent criteria for identifying tLESRs is of considerable importance in motility research. The sleeve sensor was the technological advance that led to the initial description of tLESRs and remains the only validated method for their detection. However, standardized criteria for defining tLESRs were not defined until 1995, when Holloway et al analyzed the characteristics of both deglutitive EGJ relaxation and tLESRs in 23 healthy subjects and 9 patients with gastroesophageal reflux disease (GERD). Based on that analysis, the defining characteristics of tLESRs were as follows: (1) absence of swallowing for 4 seconds before to 2 seconds after the onset of relaxation, (2) relaxation rate of ≥ 1 mm Hg/s, (3) time from onset to complete relaxation of ≤ 10 seconds, and (4) nadir pressure of ≤ 2 mm Hg.³³

Table 1. EGJ Relaxation Parameters and the Detection of Achalasia

EGJ relaxation parameter	Threshold value	Sensitivity (%)	Specificity (%)
Sleeve sensor ³²			
Basal pressure	>41 mm Hg	38	93
Mean relaxation pressure	>12 mm Hg	92	93
Percent relaxation	<57%	88	93
Relaxation duration	<2.2 seconds	31	93
High-resolution manometry with concurrent baseline ³⁴ (subjects with peristalsis)			
Lowest residual pressure	≥4 mm Hg	77	92
Lowest residual pressure over entire deglutitive period	≥4 mm Hg	68	98
Lowest mean LES relaxation pressure in a 3-second postdeglutitive interval	>10 mm Hg	85	92
High-resolution manometry with concurrent baseline ³⁴ (subjects without peristalsis)			
Lowest residual pressure	>2 mm Hg	81	89
Lowest residual pressure over entire deglutitive period	>2 mm Hg	77	89
Lowest mean LES relaxation pressure in a 3-second postdeglutitive interval	>8 mm Hg	87	95
High-resolution manometry with concurrent baseline ³⁴ (subjects with peristalsis or without peristalsis [in parentheses])			
Transsphincteric gradient	>2 mm Hg	100 (100)	85 (100)
	>5 mm Hg	94 (94)	98 (100)

NOTE. Sensitivity and specificity values are in distinguishing patients with achalasia from controls³² or mixed subject groups.³⁴

Role of Esophageal Manometry in Clinical Practice (1994–2003)

Manometry has evolved from a research tool to a diagnostic modality with wide availability. It is an excellent tool to define the integrity of peristalsis and EGJ function. However, by default, the clinical yield of esophageal manometry is limited to the detection of relatively few functional abnormalities: absent or weak peristalsis, disordered peristalsis, abnormalities of EGJ pressure, and impaired EGJ relaxation. Beyond these abnormalities, manometry also detects minor aberrations of esophageal contractility of uncertain clinical significance. In fact, unraveling the relationship between esophageal motor patterns and clinical esophageal syndromes has been the object of substantial research during the past 10 years. Thus, our objective in this section was to assess the relevance of manometric findings in the diagnosis and management of GERD, dysphagia, and chest pain. For each syndrome, relevant key words were used to search the National Library of Medicine database for the period from 1994 to 2003. The key word combination of “gastroesophageal reflux disease” and “surgery” located 492 citations, “gastroesophageal reflux” and “manometry” located 896 citations, “chest pain” and “esophageal motility disorders” located 71 citations, and “deglutition disorders” and “manometry” located 308 citations. However, papers were included in the discussion only if, in our assessment, (1) they were designed to address a clinically relevant objective, (2) the manometric findings under discussion were of potential physiologic relevance, (3) the manometric methodology used was valid, and (4) reported findings were based on an appropriate experimental design.

GERD

Diagnosis of GERD. Numerous investigations have demonstrated manometric abnormalities associated with GERD but, from a diagnostic viewpoint, the utility of each is limited by issues of sensitivity or specificity. Take, for instance, the antireflux barrier. It is logical that the severity of reflux would correlate with decreasing EGJ pressure, and to some degree this is true; a majority of studies report that patients with high-grade esophagitis or long-segment Barrett’s metaplasia have LES pressures of <10 mm Hg.^{35,36} However, other investigations emphasize that more than 60% of patients with GERD have a basal LES pressure of >10 mm Hg.³⁷ This discrepancy is partially attributable to the role of tLESRs in the pathophysiology of GERD.^{38,39} With regard to tLESRs, conventional manometric studies are too brief to adequately estimate their frequency, which ranges from 1 to 10 per hour.⁴⁰ Furthermore, the bulk of evidence suggests that it is not the absolute number of tLESRs but, rather, the proportion of tLESRs associated with acid reflux that differentiates patients with GERD from controls.⁴⁰

Similar to reduced EGJ pressure, esophageal peristaltic dysfunction is also prevalent in GERD populations. As the severity of GERD increases, the prevalence of frequent hypotensive and/or failed contractions increases.⁴¹ This, coupled with physiologic observation that contractions of <30 mm Hg are often associated with impaired volume clearance,^{21,25} led to the concept of a manometric diagnosis labeled ineffective esophageal motility (IEM), defined as the occurrence of low amplitude (<30 mm Hg) or nontransmitted contractions in the distal esophagus with 30% or more swallows.⁴² The

functional significance of IEM could relate to either dysphagia or prolonged acid clearance. With respect to acid clearance, Vinjirayer et al retrospectively compared the prevalence of IEM in patients with normal and abnormal esophageal acid exposure⁴³ and found the prevalence of IEM to be similar in each group, with no parallel between the severity of IEM and prolonged esophageal acid exposure. Although not disproving an association between IEM and GERD, that study emphasizes that peristaltic dysfunction is neither a prerequisite for GERD nor a finding unique to the GERD population. Thus, IEM joins the list of manometric aberrations associated with GERD but insufficient to establish a diagnosis of GERD.⁴⁴

Although not the subject of this review, ambulatory esophageal pH monitoring has become an increasingly common diagnostic test in the evaluation of reflux disease. The convention for performing pH monitoring studies is to position the pH probe 5 cm above the proximal margin of the LES. Suggested methodologies for pH probe placement include defining the LES by the location of the pH increase during pH electrode withdrawal, endoscopy, fluoroscopy, calculation according to subject height, or manometry. Of these methods, the manometric definition of the sphincter remains the most accurate^{45,46} except perhaps in the very young pediatric population in which subject height correlates well with esophageal length.⁴⁷ One caveat to this is that with the recently introduced Bravo wireless pH recording system, probe placement is made relative to the endoscopic localization of the squamocolumnar junction without requiring manometry.⁴⁸

Role of manometry in the management of GERD. Theoretically, identifying specific functional abnormalities in GERD could lead to customized treatment. However, the current reality is that (1) manometric parameters are poor predictors of response to therapy and (2) current pharmacologic therapy for improving either peristaltic function or EGJ pressure is very limited. Even within the context of surgical treatment with which the EGJ can be bolstered, preoperative manometric assessment is a poor predictor of outcome.⁴⁹ Rather, the best predictor of response to either antisecretory therapy or surgery is the severity of the esophagitis at index endoscopy.⁵⁰ Manometry does, however, have an important place in the preoperative assessment for antireflux surgery when uncertainty exists regarding diagnosis. Antireflux surgery will only compound a patient's problem if performed inadvertently for achalasia, scleroderma esophagus, or non-reflux-induced esophageal spasm, entities best detected by manometry.

A highly controversial issue regarding manometry in patients being considered for antireflux surgery is the relationship between preoperative peristaltic dysfunction and postoperative dysphagia, reportedly experienced in as many as 40% of patients.⁵¹⁻⁵⁴ Some experts consider impaired peristalsis to be a relative contraindication for antireflux surgery. Others have recommended that the surgery be tailored to the individual's peristaltic function, given the data suggesting that Toupet 270° fundoplication is associated with a significantly decreased incidence of dysphagia compared with Nissen 360° fundoplication.⁵³ Reasoning that the etiology of postoperative dysphagia is related to a combination of impaired peristaltic function and the relative obstruction caused by the fundoplication, this recommendation seems logical. However, currently available data contradict it. Before the publication of the first technical review in 1994, most available data relevant to this issue were either retrospective or not designed specifically to address this issue. The only relevant prospective controlled trial at that time analyzed the clinical outcome of 126 consecutive patients undergoing fundoplication without prior knowledge of their preoperative manometric findings.⁵¹ No correlation was found between preoperative manometric findings and poor surgical outcome. In fact, of the 14 patients with the most severe peristaltic function, 10 had a good response and 4 had a poor outcome but unrelated to postoperative dysphagia. This led to the highly controversial item #5 of the practice guideline accompanying the first technical review: "Manometry is possibly indicated for the preoperative assessment of peristaltic function in patients being considered for antireflux surgery and is indicated in this setting if uncertainty remains regarding the correct diagnosis."

Adding fuel to the controversy regarding the relationship between preoperative manometry and postoperative dysphagia, the past 10 years have yielded 2 prospective studies designed to address the issue. Fibbe et al prospectively studied 200 patients being considered for antireflux surgery.⁵⁴ Equal numbers of patients with and without esophageal dysmotility were prospectively randomized to either a Nissen 360° fundoplication or a Toupet 270° fundoplication. Four months postoperatively, they found that postoperative dysphagia was significantly increased among the patients who underwent Nissen fundoplication (44% Nissen vs 17% Toupet; $P < .0001$) but was unrelated to preoperative manometric findings. Another prospective trial of 106 patients randomized to either Nissen-Rosseti or a partial Toupet procedure, irrespective of their manometric findings, came to a similar conclusion.⁵⁵ Although the rate of dysphagia was similar between the 2 operations, no

correlation existed between dysphagia and preoperative manometric findings.

Taken together, the above data argue that preoperative manometry is a poor predictor of postfundoplication dysphagia. However, this conclusion must remain somewhat guarded because these studies focused on patients with mild to moderate degrees of peristaltic dysfunction, not severe dysfunction as manifest by aperistalsis. Fibbe et al found that there was a relationship between failed peristalsis and worsening dysphagia; however, dysphagia also occurred in other circumstances.⁵⁴ Ongoing research suggests that equally important considerations are the degree of constriction and the relative axial immobilization imposed on the EGJ by the fundoplication.⁵⁶ However, it is also apparent that conventional manometric techniques are insensitive to detect these underlying mechanical defects. Currently, studies assessing flow through the EGJ require a combination of fluoroscopy and high-resolution manometric evaluation. Topographic manometric data analysis and multichannel intraluminal impedance testing are also promising evolving technologies to aid in this assessment.⁵⁷

While there is much controversy regarding the role of preoperative manometry in predicting dysphagia, there is no controversy that postoperative manometry is of value for the evaluation of postoperative dysphagia. Postfundoplication dysphagia is common in the early postoperative period, and patients often require soft diets for the first 2–4 weeks. Dysphagia that persists longer than 2–4 weeks should be evaluated with an upper endoscopy or barium esophagram to assess the integrity of the wrap and evaluate for paraesophageal hernia. Subjects without an overt mechanical disruption should be evaluated with manometry to assess peristaltic function, LES pressure, and LES relaxation to assess whether the wrap is too tight or an underlying motility disorder exists.

Dysphagia

Diagnosis of dysphagia. Dysphagia is a fundamental symptom of esophageal disease and is perceived as a relative obstruction to the passage of food or liquid from the oral cavity to the stomach. Abnormal esophageal motility can cause esophageal dysphagia. However, significant esophageal motility disorders are far less common than mechanical obstruction due to peptic stricture, Schatzki ring, or mucosal inflammation from infectious, caustic, or peptic esophagitis. In fact, only after these more common entities have been excluded by endoscopy or radiographic studies should the diagnosis of a motility disorder be pursued.

Once embarking on a diagnostic pursuit of an esophageal motility disorder, the next hurdle to cross is in the

realization that identifying an abnormality on a manometric tracing does not equate to identifying a disease. To equate a manometric abnormality with an esophageal motor disorder implies that it results in a functional abnormality of either bolus transit or perception that leads to symptoms. Many manometric abnormalities, such as exaggerated contractions (nutcracker pattern or hypertensive LES), are common in both patient populations^{58–72} and healthy volunteers.^{60,61,63,71,72} Considerable attention has been directed at the functional significance of these findings, but no meaningful relationship has been established between the “abnormalities” and either specific symptoms or impaired bolus transit. Thus, this section on the use of manometry in the clinical evaluation of dysphagia focuses on manometric findings that do have a functional correlate and can cause dysphagia: achalasia and (perhaps) diffuse esophageal spasm (DES), given the limitations of that diagnosis discussed below.

Achalasia. The defining characteristics of achalasia are failure of the EGJ high-pressure zone to relax adequately with swallowing and aperistalsis in the smooth muscle esophagus. The functional significance of these manometric findings is of poor bolus transit as evident by fluoroscopy or scintigraphy. Pathologically, these findings are attributable to destruction of the inhibitory ganglionic neurons in the smooth muscle esophagus. These intramural myenteric plexus neurons mediate deglutitive inhibition (including LES relaxation) and the propagation rate of peristalsis; their absence offers a unifying hypothesis for the key physiologic abnormalities of achalasia: impaired LES relaxation and aperistalsis. Other manometric features (elevated intraesophageal pressure, hypertensive LES, or isobaric waveforms) provide supportive evidence to substantiate the diagnosis of achalasia but are not essential findings.⁷³

Given that esophageal aperistalsis also occurs with disorders other than achalasia, including GERD, collagen vascular diseases, and diabetes, the diagnosis of achalasia is highly dependent on accurately detecting impaired LES relaxation. Assuming that the LES could be intubated, an inaccurate diagnosis of impaired relaxation could result from artifactual relaxation associated with inappropriate catheter design or from using suboptimal diagnostic thresholds. Two studies utilizing assemblies that control for the effect of axial movement (a sleeve sensor and high-resolution manometry with topographic analysis) were recently conducted to minimize such errors. The highlights of these studies are summarized in [Table 1](#). With a sleeve sensor, the best single assessment of EGJ relaxation for a diagnosis of achalasia was mean relaxation pressure using the 95th percentile

value of controls (12 mm Hg) as the upper limit of normal.³² Utilizing high-resolution manometry with topographic analysis, similar accuracy was achieved using a threshold value of 8–10 mm Hg for the lowest mean residual pressure in a 3-second postdeglutitive interval.³⁴ However, the greatest accuracy was achieved utilizing a novel concept for assessing LES relaxation: the trans-sphincteric pressure gradient during the 2- to 6-second postswallow interval. Pressure gradients exceeding 5 mm Hg had a sensitivity of 94% and a specificity of 98% for detecting achalasia.

Although utilizing the methods and thresholds defined in Table 1 will maximize diagnostic accuracy, manometry remains an imperfect tool for detecting achalasia. Manometric variants exist in achalasia that can still confound the diagnosis.^{74–76} Illustrative of this is a report describing 4 achalasia variants in a retrospective study of 58 patients with idiopathic achalasia.⁷⁷ Achalasia variants were characterized by (1) high-amplitude esophageal body contractions (“vigorous achalasia”), (2) retained peristalsis in most of the esophagus with only a short segment of aperistalsis, (3) retained deglutitive LES relaxation, and (4) impaired deglutitive relaxation but intact tLESRs. Despite utilizing state-of-the-art technique, each of these achalasia variants had atypical features of either peristalsis or LES relaxation confounding its diagnosis. Nonetheless, in each case, the patients were symptomatically improved following Heller myotomy, and histopathologic analysis subsequently confirmed inflammation and destruction of the myenteric plexus. In addition to the possibility of misdiagnosis, manometric criteria of achalasia are not 100% specific for either idiopathic achalasia or Chagas’ disease. Pseudoachalasia accounts for up to 5% of cases with manometric criteria typifying achalasia, being more common with progressive age.⁷⁸

DES. DES is defined as a clinical entity associated with abnormal esophageal contractions causing dysphagia and/or chest pain. Although the etiology is unclear, it likely represents a selective, often intermittent, dysfunction of the myenteric plexus.^{79,80} However, unlike achalasia (and akin to nonspecific esophageal motility disorders), DES is defined by manometric criteria rather than by clinical, functional, or pathologic criteria. It also differs from achalasia in that it is usually an intermittent phenomenon, with the esophagus alternatively exhibiting normal primary peristalsis. Partly because of these features, the diagnostic criteria for DES are a subject of increasing controversy.

The manometric feature universal among proposed classification schemes for DES is the occurrence of simultaneous contractions.⁶² However, beyond that there is

little agreement as to how frequently such contractions need to occur or whether they must exceed a threshold amplitude to qualify.⁸¹ With respect to frequency, the observation that simultaneous contractions with $\geq 20\%$ of swallows have not been found in healthy volunteers argues in favor of accepting that threshold. As for an appropriate threshold amplitude for what constitutes a “spastic” contraction, simultaneous low-amplitude contractions occur in scleroderma, amyloidosis, pseudo-obstruction, alcoholic neuropathies, and GERD, all entities from which DES should be distinguished. Recognizing that the functional significance of these low-amplitude pressure waves is different from that of high-amplitude contractions, Spechler and Castell recently proposed adding a second necessary manometric criterion for DES that would incorporate a minimum amplitude of 20 mm Hg for simultaneous contractions, based on functional studies assessing bolus transit.⁸² Although this added manometric criterion should improve the specificity of manometry in detecting DES, it may still be too inclusive, thereby perpetuating the overdiagnosis of DES.

The broader issue that has emerged is whether or not DES even merits recognition as a major esophageal motor disorder any more than do other manometrically defined conditions without clear functional correlates, specifically nutcracker esophagus, hypertensive LES, and non-specific esophageal motor disorders. Clearly, if one applies a permissive definition to DES, the answer to this is no. On the other hand, if one applies a very restrictive definition, DES becomes so rare that its very existence comes into question. Such a definition would require the presence of esophageal contractions of excessive amplitude and duration temporally associated with symptoms (chest pain, dysphagia) in association with normal LES relaxation. Applying this restrictive definition in the setting of ambulatory manometry (to increase the yield for symptom correlation), Barham et al found that only 16 of 390 symptomatic patients reported symptoms that were correlated with spastic events.⁸³ These events met any criteria for spastic contractions but, given the rarity with which they were observed, it seems somewhat likely that they represent an occasional manifestation of another disease process such as reflux rather than a distinct clinical entity. Yet another consideration is that, in some instances, DES is associated with incomplete LES relaxation, in which case it is likely a variant of achalasia.⁷⁷ Taken together, these observations suggest that if DES is a distinct major motor disorder, it is certainly extremely rare. Traditional manometric criteria have oversimplified the problem, resulting in overdiagnosis of the entity.

Role of manometry in the management of dysphagia. Treatment of achalasia results in symptomatic and functional improvement, making its identification of indisputable clinical significance. Therapy is focused on relieving the obstruction associated with incomplete LES relaxation, be that by pneumatic dilatation, Heller myotomy, or pharmacologic therapy. However, currently there are no pretreatment manometric characteristics that define which therapy is most appropriate for a given patient.

With respect to evaluating patients with a suboptimal response to achalasia treatment, surgical failure may result from an incomplete myotomy, scarring, functional obstruction by the antireflux component of the surgery, paraesophageal hernia, or profound esophageal dilatation. Similarly, failure after pneumatic dilatation may result from inadequate disruption of the LES or profound esophageal dilatation. Limited data suggest that manometry can improve operative outcome with Heller myotomy by minimizing the occurrence of incomplete myotomy.^{84,85} Even in reports emanating from large referral centers, incomplete myotomy is noted to occur in up to 13% of patients.^{85,86} Intraoperative manometry as an adjunct to Heller myotomy was the subject of a recent report on 139 patients with achalasia.⁸⁷ In that report, intraoperative manometry detected a residual EGJ high pressure in 45 subjects, leading to extension or modification of the myotomy. Thirty-one of these instances were noted in the first 70 patients in the series, reflecting on the learning curve for this operation. At 1-month follow-up, 126 subjects had responded to myotomy (93%) with only one subject failing because of persistent EGJ high pressure.

Manometry is useful in evaluating symptomatic patients after Heller myotomy or pneumatic dilation. Data suggest that relief of dysphagia is related to postprocedure EGJ pressure, with a value of <10 mm Hg being optimal.⁸⁸ Identification of residual EGJ high pressure >10 mm Hg argues for further therapy targeting LES disruption. On the other hand, symptomatic subjects with basal LES pressures of <10 mm Hg may not benefit from repeat dilation or surgery and should be evaluated with a timed barium swallow to assess emptying.⁸⁹ In instances in which a timed barium swallow demonstrates poor esophageal emptying despite an optimal reduction of EGJ pressure, esophageal resection with gastric pull-up or colon interposition may be indicated.

The role of manometry in the management of dysphagia associated with DES is limited by the fact that the disease is poorly defined and that there are no controlled trials demonstrating efficacy of any therapeutic regimen. There are no reliable manometric thresholds that corre-

late with symptom improvement, and data suggest that there is no correlation between symptom improvement and pharmacologic reduction of contraction amplitude.

Chest Pain

Diagnosis of chest pain. The most controversial application of esophageal manometry pertains to the evaluation of chest pain. Abnormal esophageal motor function exemplified by achalasia, DES, or GERD may lead to chest pain primarily through sensation of mechanical effects on the muscular wall or indirectly through its inability to protect and defend the esophagus from noxious irritant stimuli (GERD). However, as tabulated in the first technical review, even though manometric abnormalities are frequently encountered in patients with chest pain, the manometric patterns of achalasia and DES account for only a small percentage.² Rather, most patients with chest pain are found to have "nonspecific disorders" such as those associated with exaggerated contractions in the esophageal body (nutcracker esophagus, hypertensive LES)⁶⁵ or those associated with hypotensive contractions, such as a hypotensive LES.⁹⁰ Carefully weighing the evidence regarding the clinical relevance of these findings led to the highly controversial item #7 of the practice recommendations emanating from the first technical review: "Manometry should not be routinely used as the initial test for chest pain or other esophageal symptoms because of the low specificity of the findings and the low likelihood of detecting a clinically significant motility disorder." Rather than review the data leading to the conclusion that "nonspecific motility disorders" had little clinical relevance, the following section details the evolution of thinking on the link between the esophagus and chest pain since 1994.

After the realization that manometrically detected "nonspecific esophageal motor disorders" were at best an epiphenomenon in patients with chest pain, investigations into other possible links between the esophagus and chest pain have focused on 3 hypotheses: (1) chest pain is a manifestation of reflux, (2) pain is attributable to abnormal motor events but the events are sufficiently infrequent so that they are not easily detected on bedside manometry, and (3) pain is esophageal in origin but not a direct consequence of the motor events detected at manometry. Each of these possibilities will be reviewed.

The relationship between GERD and chest pain has been recognized since the original description of the Bernstein test. In fact, gastroesophageal reflux is probably the most common esophageal motor disorder associated with chest pain.^{68,69,91-95} In 1982, Demeester et al reported that up to 46% of patients discharged from a

coronary care unit with a diagnosis of noncardiac chest pain had abnormal gastroesophageal reflux.⁹¹ Several studies have subsequently confirmed a high prevalence of abnormal acid exposure in patients with noncardiac chest pain.^{69,95-98} In terms of therapy, both surgical and medical approaches have concluded that the most useful therapy in patients with chest pain, regardless of a concomitant nonspecific motor disorder, was directed at controlling reflux.^{64,94,99,100} In addition, a therapeutic trial with potent antisecretory therapy is a useful cost-effective diagnostic method. Fass et al reported that the "omeprazole test" (40 mg AM and 20 mg PM for 7 days) had a sensitivity of 78% and a specificity of 86%.¹⁰¹ Although not quite as accurate as standard ambulatory pH monitoring, the investigators estimated that the omeprazole test might save \$573 per average patient and result in a 59% reduction in the number of diagnostic tests. Thus, a therapeutic trial with potent antisecretory therapy, such as proton pump inhibitors, should be considered before an aggressive evaluation of esophageal function is performed.

Because both chest pain and abnormal peristaltic contractions are sporadic events, the likelihood of documenting both in a brief bedside study seems slim. This perception fostered the development of ambulatory esophageal manometry systems capable of longer recording intervals with the hope of correlating sporadic symptoms with sporadic contractile events. However, despite several examinations of this technology, no consensus has emerged regarding scoring techniques or overall utility. One study using combined ambulatory manometry and pH studies on a highly selected group of patients acutely hospitalized for attacks of chest pain showed that up to 43% of patients have pain associated with episodes of acid reflux, but there was little additional yield from the manometric data.¹⁰² On the other hand, another trial did detect sporadic symptomatic spastic events. Barham et al compared 24-hour ambulatory manometry with standard laboratory-based manometry in detecting DES as a cause of chest pain.⁸³ They reported that 16 of 390 patients (4%) were classified as having DES by 24-hour monitoring on the basis of painful events concomitant with contractions of excessive duration and amplitude. In contrast, standard manometry detected only 2 of these 16 patients and incorrectly labeled an additional 53 (14%) as having DES on the basis of asymptomatic manometric criteria. The variability of these results can be explained by differences in patient populations studied and analysis schemes utilized. Thus, at present, ambulatory manometry remains an investigational technique with scoring criteria and symptom-association criteria remaining to be established.

The final hypothesis to be explored linking chest pain to the esophagus is that although the esophagus is the ultimate cause of chest pain, the relevant findings are not evident with conventional manometry. Using high-frequency intraesophageal ultrasonography, Balaban et al reported a high correlation between chest pain events and sustained esophageal muscular contractions.¹⁰³ The contractions were likely to reflect longitudinal muscle contraction because they were not associated with lumen closure and changes in intraluminal pressure. This phenomenon would therefore not be evident during conventional manometric monitoring. Alternatively, the relevant parameter could be abnormal sensitivity or compliance. Richter et al first reported that balloon distention reproduced chest pain in a higher proportion of patients with chest pain compared with healthy controls (60% vs 20%, $P < .05$).¹⁰⁴ The past 10 years have seen a dramatic increase in the sophistication of studies assessing balloon distention and biomechanical properties of the esophagus. One recent advance, impedance planimetry, is a method designed to measure simultaneous intraluminal pressure and cross-sectional area. Using this technique, Rao et al reported that chest pain patients without GERD have a stiffer and less distensible esophagus than healthy volunteers.^{105,106} In addition, threshold sensation and threshold discomfort occurred at significantly lower pressures and circumferential wall tension levels in patients compared with controls. Even after inhibiting smooth muscle activity with atropine, balloon distention still induced chest pain at these lower pressures.¹⁰⁶ Furthermore, the pressure and wall tension thresholds required to generate moderate discomfort and pain were significantly lower after treatment with atropine, suggesting that this response may be mediated by stretch instead of abnormal muscular contraction. Although these studies have added significantly to our understanding of the pathogenesis of esophageal chest pain, there is currently no validated clinical use for impedance planimetry and it remains an experimental technique.

Management of chest pain. Contrary to practice patterns of the recent past, recent data suggest that the role of manometry in the evaluation of patients with chest pain is limited to patients who have been sufficiently evaluated and treated for GERD and those in whom achalasia is a possible diagnosis. Certainly, abnormal gastroesophageal reflux is the most common esophageal etiology of esophageal chest pain and antireflux therapy offers the most potential benefit in terms of symptom response. At present, no data exist comparing ambulatory pH monitoring with an empiric trial of antireflux therapy in this application and either approach

would be appropriate before consideration of an esophageal motor disorder.

Patients who do not respond to antireflux therapy or patients in whom the clinical suspicion of achalasia is high may benefit from manometric evaluation, realizing that the yield is low. Identification of achalasia has important clinical ramifications because treatment results in significant improvement in dysphagia. This is less straightforward with chest pain that is less likely to respond to achalasia treatment.¹⁰⁷

Manometry for the Diagnosis of Multisystem Disease

Manometrically evident abnormalities of peristalsis and LES function can be associated with systemic diseases that affect smooth muscle or the autonomic nervous system. The pattern of dysfunction evident in scleroderma and other collagen vascular diseases is of diminished or absent peristalsis in the distal half to two thirds of the esophagus and diminished or absent LES pressure with preserved function in the proximal third of the esophagus and the UES.¹⁰⁸ Clinically, this often results in dysphagia and GERD along with its complications. These findings are so characteristic of scleroderma that this manometric pattern has been labeled "scleroderma esophagus." However, scleroderma esophagus is neither sensitive nor specific for collagen vascular diseases and can be found in GERD patients without scleroderma. Although the relationship between esophageal dysmotility and collagen vascular disease is strong, it was the fact that esophageal dysmotility was part of the diagnostic criteria of the CREST syndrome that led to the previous guideline recommendation #3: "Manometry is indicated for detecting esophageal motor abnormalities associated with systemic diseases (eg, connective tissue diseases) if their detection would contribute to establishing a multisystem diagnosis or other aspects of management." Recent changes in the diagnostic criteria of scleroderma and the lack of clinical data demonstrating clinical benefit from the routine evaluation of patients without esophageal symptoms require reevaluation of this guideline. The CREST syndrome is no longer considered a distinct clinical entity with a distinct management strategy.^{6,109} Given these events, it is reasonable to omit a specific guideline for the clinical use of esophageal manometry addressing collagen vascular disease and to instead manage these patients on a symptomatic basis.

JOHN E. PANDOLFINO
PETER J. KAHRILAS
*Northwestern University
Chicago, Illinois*

References

1. An American Gastroenterological Association medical position statement on the clinical use of esophageal manometry. *American Gastroenterological Association. Gastroenterology* 1994;107:1865.
2. Kahrilas PJ, Clouse RE, Hogan WJ. American Gastroenterological Association technical review on the clinical use of esophageal manometry. *Gastroenterology* 1994;107:1865-1884.
3. Orłowski J, Dodds WJ, Linehan JH, Dent J, Hogan WJ, Arndorfer RC. Requirements for accurate manometric recording of pharyngeal and esophageal peristaltic pressure waves. *Invest Radiol* 1982;17:567-572.
4. Schoeman MN, Tippet MD, Akkermans LM, Dent J, Holloway RH. Mechanisms of gastroesophageal reflux in ambulant healthy human subjects. *Gastroenterology* 1995;108:83-91.
5. van Herwaarden MA, Samsom M, Smout AJ. Excess gastroesophageal reflux in patients with hiatus hernia is caused by mechanisms other than transient LES relaxations. *Gastroenterology* 2000;119:1439-1446.
6. Murray JA, Clouse RE, Conklin JL. Components of the standard esophageal manometry. *Neurogastroenterol Motil* 2003;15:591-606.
7. Clouse RE, Staiano A, Alrakawi A. Development of a topographic analysis system for manometric studies in the gastrointestinal tract. *Gastrointest Endosc* 1998;48:395-401.
8. Holloway RH. Topographical clinical esophageal manometry: a better mousetrap or manometric overkill? *Am J Gastroenterol* 2000;95:2677-2679.
9. Fass J, Silny J, Braun J, Heindrichs U, Dreu B, Schumpelick V, Rau G. Measuring esophageal motility with a new intraluminal impedance device. First clinical results in reflux patients. *Scand J Gastroenterol* 1994;29:693-702.
10. Nguyen HN, Silny J, Albers D, Roeb E, Gartung C, Rau G, Matern S. Dynamics of esophageal bolus transport in healthy subjects studied using multiple intraluminal impedancometry. *Am J Physiol* 1997;273:G958-G964.
11. Srinivasan R, Vela MF, Katz PO, Tutuian R, Castell JA, Castell DO. Esophageal function testing using multichannel intraluminal impedance. *Am J Physiol Gastrointest Liver Physiol* 2001;280:G457-G462.
12. Simren M, Silny J, Holloway R, Tack J, Janssens J, Sifrim D. Relevance of ineffective oesophageal motility during oesophageal acid clearance. *Gut* 2003;52:784-790.
13. Sifrim D, Castell DO, Dent J, Kahrilas PJ. Gastro-oesophageal reflux monitoring: review and consensus report on detection and definitions of acid, non-acid and gas reflux. *Gut* 2004;53:1024-1031.
14. Kahrilas PJ, Dodds WJ, Dent J, Logemann JA, Shaker R. Upper esophageal sphincter function during deglutition. *Gastroenterology* 1988;95:52-62.
15. Welch RW, Luckmann K, Ricks PM, Drake ST, Gates GA. Manometry of the normal upper esophageal sphincter and its alterations in laryngectomy. *J Clin Invest* 1979;63:1036-1041.
16. Dire C, Shi G, Manka M, Kahrilas PJ. Manometric characteristics of the upper esophageal sphincter recorded with a microsleeve. *Am J Gastroenterol* 2001;96:1383-1389.
17. Castell JA, Castell DO. Modern solid state computerized manometry of the pharyngo-oesophageal segment. *Dysphagia* 1993;8:270-275.
18. Malhi-Chowla N, Achem SR, Stark ME, DeVault KR. Manometry of the upper esophageal sphincter and pharynx is not useful in unselected patients referred for esophageal testing. *Am J Gastroenterol* 2000;95:1417-1421.
19. Dantas RO, Cook IJ, Dodds WJ, Kern MK, Lang IM, Brasseur JG. Biomechanics of cricopharyngeal bars. *Gastroenterology* 1990;99:1269-1274.

20. Pal A, Williams RB, Cook IJ, Brasseur JG. Intrabolus pressure gradient identifies pathological constriction in the upper esophageal sphincter during flow. *Am J Physiol Gastrointest Liver Physiol* 2003;285:G1037–G1048.
21. Kahrilas PJ, Dodds WJ, Hogan WJ. Effect of peristaltic dysfunction on esophageal volume clearance. *Gastroenterology* 1988;94:73–80.
22. Clouse RE, Staiano A. Topography of the esophageal peristaltic pressure wave. *Am J Physiol* 1991;261:G677–G684.
23. Clouse RE, Staiano A. Topography of normal and high-amplitude esophageal peristalsis. *Am J Physiol* 1993;265:G1098–G1107.
24. Clouse RE, Staiano A, Alrakawi A. Topographic analysis of esophageal double-peaked waves. *Gastroenterology* 2000;118:469–476.
25. Tutuian R, Castell DO. Clarification of the esophageal function defect in patients with manometric ineffective esophageal motility: studies using combined impedance-manometry. *Clin Gastroenterol Hepatol* 2004;2:230–236.
26. Liu J, Parashar VK, Mittal RK. Asymmetry of lower esophageal sphincter pressure: is it related to the muscle thickness or its shape? *Am J Physiol* 1997;272:G1509–G1517.
27. Kahrilas PJ, Lin S, Chen J, Manka M. The effect of hiatus hernia on gastro-oesophageal junction pressure. *Gut* 1999;44:476–482.
28. Goyal RK, Sangree MH, Hersh T, Spiro HM. Pressure inversion point at the upper high pressure zone and its genesis. *Gastroenterology* 1970;59:754–759.
29. Holloway RH, Blank EL, Takahashi I, Dodds WJ, Dent J, Sarna SK. Electrical control activity of the lower esophageal sphincter in unanesthetized opossums. *Am J Physiol* 1987;252:G511–G521.
30. Mittal RK, Rochester DF, McCallum RW. Electrical and mechanical activity in the human lower esophageal sphincter during diaphragmatic contraction. *J Clin Invest* 1988;81:1182–1189.
31. Richter JE, Wu WC, Johns DN, Blackwell JN, Nelson JL III, Castell JA, Castell DO. Esophageal manometry in 95 healthy adult volunteers. Variability of pressures with age and frequency of “abnormal” contractions. *Dig Dis Sci* 1987;32:583–592.
32. Shi G, Ergun GA, Manka M, Kahrilas PJ. Lower esophageal sphincter relaxation characteristics using a sleeve sensor in clinical manometry. *Am J Gastroenterol* 1998;93:2373–2379.
33. Holloway RH, Penagini R, Ireland AC. Criteria for objective definition of transient lower esophageal sphincter relaxation. *Am J Physiol* 1995;268:G128–G133.
34. Staiano A, Clouse RE. Detection of incomplete lower esophageal sphincter relaxation with conventional point-pressure sensors. *Am J Gastroenterol* 2001;96:3258–3267.
35. Coenraad M, Masclee AA, Straathof JW, Ganesh S, Griffioen G, Lamers CB. Is Barrett’s esophagus characterized by more pronounced acid reflux than severe esophagitis? *Am J Gastroenterol* 1998;93:1068–1072.
36. Loughney T, Maydonovitch CL, Wong RK. Esophageal manometry and ambulatory 24-hour pH monitoring in patients with short and long segment Barrett’s esophagus. *Am J Gastroenterol* 1998;93:916–919.
37. Behar J, Biancani P, Sheahan DG. Evaluation of esophageal tests in the diagnosis of reflux esophagitis. *Gastroenterology* 1976;71:9–15.
38. Dent J, Dodds WJ, Friedman RH, Sekiguchi T, Hogan WJ, Arndorfer RC, Petrie DJ. Mechanism of gastroesophageal reflux in recumbent asymptomatic human subjects. *J Clin Invest* 1980;65:256–267.
39. Dodds WJ, Dent J, Hogan WJ, Helm JF, Hauser R, Patel GK, Egide MS. Mechanisms of gastroesophageal reflux in patients with reflux esophagitis. *N Engl J Med* 1982;307:1547–1552.
40. Sifrim D, Holloway R. Transient lower esophageal sphincter relaxations: how many or how harmful? *Am J Gastroenterol* 2001;96:2529–2532.
41. Kahrilas PJ, Dodds WJ, Hogan WJ, Kern M, Arndorfer RC, Reece A. Esophageal peristaltic dysfunction in peptic esophagitis. *Gastroenterology* 1986;91:897–904.
42. Leite LP, Johnston BT, Barrett J, Castell JA, Castell DO. Ineffective esophageal motility (IEM): the primary finding in patients with nonspecific esophageal motility disorder. *Dig Dis Sci* 1997;42:1859–1865.
43. Vinjirayer E, Gonzalez B, Brensinger C, Bracy N, Obelmeijas R, Katzka DA, Metz DC. Ineffective motility is not a marker for gastroesophageal reflux disease. *Am J Gastroenterol* 2003;98:771–776.
44. Kahrilas PJ, Pandolfino JE. Ineffective esophageal motility does not equate to GERD. *Am J Gastroenterol* 2003;98:715–717.
45. Mattox HE III, Richter JE. Manometry vs. pH step-up. *Am J Gastroenterol* 1991;86:1280–1282.
46. Klauser AG, Schindlbeck NE, Muller-Lissner SA. Esophageal 24-h pH monitoring: is prior manometry necessary for correct positioning of the electrode? *Am J Gastroenterol* 1990;85:1463–1467.
47. Staiano A, Clouse RE. Value of subject height in predicting lower esophageal sphincter location. *Am J Dis Child* 1991;145:1424–1427.
48. Pandolfino JE, Richter JE, Ours T, Guardino JM, Chapman J, Kahrilas PJ. Ambulatory esophageal pH monitoring using a wireless system. *Am J Gastroenterol* 2003;98:740–749.
49. Patti MG, Perretta S, Fisichella PM, D’Avanzo A, Galvani C, Gorodner V, Way LW. Laparoscopic antireflux surgery: preoperative lower esophageal sphincter pressure does not affect outcome. *Surg Endosc* 2003;17:386–389.
50. Bell NJ, Hunt RH. Role of gastric acid suppression in the treatment of gastro-oesophageal reflux disease. *Gut* 1992;33:118–124.
51. Mughal MM, Bancewicz J, Marples M. Oesophageal manometry and pH recording does not predict the bad results of Nissen fundoplication. *Br J Surg* 1990;77:43–45.
52. Spechler SJ. Comparison of medical and surgical therapy for complicated gastroesophageal reflux disease in veterans. The Department of Veterans Affairs Gastroesophageal Reflux Disease Study Group. *N Engl J Med* 1992;326:786–792.
53. Lund RJ, Wetcher GJ, Raiser F, Glaser K, Perdakis G, Gadenstatter M, Katada N, Filipi CJ, Hinder RA. Laparoscopic Toupet fundoplication for gastroesophageal reflux disease with poor esophageal body motility. *J Gastrointest Surg* 1997;1:301–308.
54. Fibbe C, Layer P, Keller J, Strate U, Emmermann A, Zornig C. Esophageal motility in reflux disease before and after fundoplication: a prospective, randomized, clinical, and manometric study. *Gastroenterology* 2001;121:5–14.
55. Rydberg L, Ruth M, Abrahamsson H, Lundell L. Tailoring antireflux surgery: a randomized clinical trial. *World J Surg* 1999;23:612–618.
56. Kahrilas PJ, Lin S, Spiess AE, Brasseur JG, Joehl RJ, Manka M. Impact of fundoplication on bolus transit across esophagogastric junction. *Am J Physiol* 1998;275:G1386–G1393.
57. Castell DO. Esophageal manometry prior to antireflux surgery: required, preferred, or even needed? [comment]. *Gastroenterology* 2001;121:214–216.
58. Ferguson SC, Hodges K, Hersh T, Jinich H. Esophageal manometry in patients with chest pain and normal coronary arteriogram. *Am J Gastroenterol* 1981;75:124–127.
59. Meshkinpour H, Glick ME, Sanchez P, Tarvin J. Esophageal manometry: a benefit and cost analysis. *Dig Dis Sci* 1982;27:772–775.
60. Traube M, Albibi R, McCallum RW. High-amplitude peristaltic esophageal contractions associated with chest pain. *JAMA* 1983;250:2655–2659.
61. Benjamin SB, Richter JE, Cordova CM, Knuff TE, Castell DO. Prospective manometric evaluation with pharmacologic provo-

- cation of patients with suspected esophageal motility dysfunction. *Gastroenterology* 1983;84:893-901.
62. Richter JE, Castell DO. Diffuse esophageal spasm: a reappraisal. *Ann Intern Med* 1984;100:242-245.
 63. Herrington JP, Burns TW, Balart LA. Chest pain and dysphagia in patients with prolonged peristaltic contractile duration of the esophagus. *Dig Dis Sci* 1984;29:134-140.
 64. Bancewicz J, Osugi H, Marples M. Clinical implications of abnormal oesophageal motility. *Br J Surg* 1987;74:416-419.
 65. Katz PO, Dalton CB, Richter JE, Wu WC, Castell DO. Esophageal testing of patients with noncardiac chest pain or dysphagia. Results of three years' experience with 1161 patients. *Ann Intern Med* 1987;106:593-597.
 66. Breumelhof R, Nadorp JH, Akkermans LM, Smout AJ. Analysis of 24-hour esophageal pressure and pH data in unselected patients with noncardiac chest pain. *Gastroenterology* 1990;99:1257-1264.
 67. Hewson EG, Dalton CB, Hackshaw BT, Wu WC, Richter JE. The prevalence of abnormal esophageal test results in patients with cardiovascular disease and unexplained chest pain. *Arch Intern Med* 1990;150:965-969.
 68. Garcia-Pulido J, Patel PH, Hunter WC, Douglas JE, Thomas E. Esophageal contribution to chest pain in patients with coronary artery disease. *Chest* 1990;98:806-810.
 69. Hewson EG, Sinclair JW, Dalton CB, Richter JE. Twenty-four-hour esophageal pH monitoring: the most useful test for evaluating noncardiac chest pain. *Am J Med* 1991;90:576-583.
 70. Hsia PC, Maher KA, Lewis JH, Cattau EL Jr, Fleischer DE, Benjamin SB. Utility of upper endoscopy in the evaluation of noncardiac chest pain. *Gastrointest Endosc* 1991;37:22-6.
 71. Clouse RE, Staiano A. Manometric patterns using esophageal body and lower sphincter characteristics. Findings in 1013 patients. *Dig Dis Sci* 1992;37:289-296.
 72. Bassotti G, Pelli MA, Morelli A. Esophageal motor disorders in patients evaluated for dysphagia and/or noncardiac chest pain. *Dysphagia* 1992;7:3-7.
 73. McCord GS, Staiano A, Clouse RE. Achalasia, diffuse spasm and non-specific motor disorders. *Baillieres Clin Gastroenterol* 1991;5:307-335.
 74. Vantrappen G, Janssens J, Hellemans J, Coremans G. Achalasia, diffuse esophageal spasm, and related motility disorders. *Gastroenterology* 1979;76:450-457.
 75. Katz PO, Richter JE, Cowan R, Castell DO. Apparent complete lower esophageal sphincter relaxation in achalasia. *Gastroenterology* 1986;90:978-983.
 76. Goldenberg SP, Burrell M, Fette GG, Vos C, Traube M. Classic and vigorous achalasia: a comparison of manometric, radiographic, and clinical findings. *Gastroenterology* 1991;101:743-748.
 77. Hirano I, Tatum RP, Shi G, Sang Q, Joehl RJ, Kahrilas PJ. Manometric heterogeneity in patients with idiopathic achalasia. *Gastroenterology* 2001;120:789-798.
 78. Kahrilas PJ, Kishk SM, Helm JF, Dodds WJ, Harig JM, Hogan WJ. Comparison of pseudoachalasia and achalasia. *Am J Med* 1987;82:439-446.
 79. Behar J, Biancani P. Pathogenesis of simultaneous esophageal contractions in patients with motility disorders. *Gastroenterology* 1993;105:111-118.
 80. Sifrim D, Janssens J, Vantrappen G. Failing deglutitive inhibition in primary esophageal motility disorders. *Gastroenterology* 1994;106:875-882.
 81. Allen ML, DiMarino AJ Jr. Manometric diagnosis of diffuse esophageal spasm. *Dig Dis Sci* 1996;41:1346-1349.
 82. Spechler SJ, Castell DO. Classification of oesophageal motility abnormalities. *Gut* 2001;49:145-151.
 83. Barham CP, Gotley DC, Fowler A, Mills A, Alderson D. Diffuse oesophageal spasm: diagnosis by ambulatory 24 hour manometry. *Gut* 1997;41:151-155.
 84. Tatum RP, Kahrilas PJ, Manka M, Joehl RJ. Operative manometry and endoscopy during laparoscopic Heller myotomy. An initial experience. *Surg Endosc* 1999;13:1015-1020.
 85. Nussbaum MS, Jones MP, Pritts TA, Fischer DR, Wabnitz B, Bondi J. Intraoperative manometry to assess the esophagogastric junction during laparoscopic fundoplication and myotomy. *Surg Laparosc Endosc Percutan Tech* 2001;11:294-300.
 86. Patti MG, Pellegrini CA, Horgan S, Arcerito M, Omelanczuk P, Tamburini A, Diener U, Eubanks TR, Way LW. Minimally invasive surgery for achalasia: an 8-year experience with 168 patients. *Ann Surg* 1999;230:587-593; discussion 593-594.
 87. Chapman J, Joehl RJ, Murayama KM, Tatum RP, Shi G, Hirano I, Jones MP, Pandolfino JE, Kahrilas PJ. Achalasia treatment: improved outcome of laparoscopic myotomy with operative manometry. *Arch Surg* 2004;139:508-513.
 88. Eckardt VF, Aignherr C, Bernhard G. Predictors of outcome in patients with achalasia treated by pneumatic dilation. *Gastroenterology* 1992;103:1732-1738.
 89. Vaezi MF, Baker ME, Achkar E, Richter JE. Timed barium oesophagram: better predictor of long term success after pneumatic dilation in achalasia than symptom assessment. *Gut* 2002;50:765-770.
 90. Dekel R, Pearson T, Wendel C, De Garmo P, Fennerty MB, Fass R. Assessment of oesophageal motor function in patients with dysphagia or chest pain—the Clinical Outcomes Research Initiative experience. *Aliment Pharmacol Ther* 2003;18:1083-1089.
 91. DeMeester TR, O'Sullivan GC, Bermudez G, Midell AI, Cimochoowski GE, O'Drobinak J. Esophageal function in patients with angina-type chest pain and normal coronary angiograms. *Ann Surg* 1982;196:488-498.
 92. de Caestecker JS, Blackwell JN, Brown J, Heading RC. The oesophagus as a cause of recurrent chest pain: which patients should be investigated and which tests should be used? *Lancet* 1985;2:1143-1146.
 93. Janssens J, Vantrappen G, Ghillebert G. 24-hour recording of esophageal pressure and pH in patients with noncardiac chest pain. *Gastroenterology* 1986;90:1978-1984.
 94. Singh S, Richter JE, Hewson EG, Sinclair JW, Hackshaw BT. The contribution of gastroesophageal reflux to chest pain in patients with coronary artery disease. *Ann Intern Med* 1992;117:824-830.
 95. Cooke RA, Anggiansah A, Chambers JB, Owen WJ. A prospective study of oesophageal function in patients with normal coronary angiograms and controls with angina. *Gut* 1998;42:323-329.
 96. Nevens F, Janssens J, Piessens J, Ghillebert G, De Geest H, Vantrappen G. Prospective study on prevalence of esophageal chest pain in patients referred on an elective basis to a cardiac unit for suspected myocardial ischemia. *Dig Dis Sci* 1991;36:229-235.
 97. Ghillebert G, Janssens J, Vantrappen G, Nevens F, Piessens J. Ambulatory 24 hour intraoesophageal pH and pressure recordings v provocation tests in the diagnosis of chest pain of oesophageal origin. *Gut* 1990;31:738-744.
 98. Fass R, Fennerty MB, Ofman JJ, Gralnek IM, Johnson C, Camargo E, Sampliner RE. The clinical and economic value of a short course of omeprazole in patients with noncardiac chest pain. *Gastroenterology* 1998;115:42-49.
 99. Achem SR, Kolts BE, Wears R, Burton L, Richter JE. Chest pain associated with nutcracker esophagus: a preliminary study of the role of gastroesophageal reflux. *Am J Gastroenterol* 1993;88:187-192.
 100. Achem SR, Kolts BE, MacMath T, Richter J, Mohr D, Burton L, Castell DO. Effects of omeprazole versus placebo in treatment of noncardiac chest pain and gastroesophageal reflux. *Dig Dis Sci* 1997;42:2138-2145.
 101. Fass R, Ofman JJ, Gralnek IM, Johnson C, Camargo E, Sampliner RE, Fennerty MB. Clinical and economic assessment

- of the omeprazole test in patients with symptoms suggestive of gastroesophageal reflux disease. *Arch Intern Med* 1999;159:2161–2168.
102. Lam HG, Dekker W, Kan G, Breedijk M, Smout AJ. Acute non-cardiac chest pain in a coronary care unit. Evaluation by 24-hour pressure and pH recording of the esophagus. *Gastroenterology* 1992;102:453–460.
103. Balaban DH, Yamamoto Y, Liu J, Pehlivanov N, Wisniewski R, DeSilvey D, Mittal RK. Sustained esophageal contraction: a marker of esophageal chest pain identified by intraluminal ultrasonography. *Gastroenterology* 1999;116:29–37.
104. Richter JE, Barish CF, Castell DO. Abnormal sensory perception in patients with esophageal chest pain. *Gastroenterology* 1986;91:845–852.
105. Rao SS, Gregersen H, Hayek B, Summers RW, Christensen J. Unexplained chest pain: the hypersensitive, hyperreactive, and poorly compliant esophagus. *Ann Intern Med* 1996;124:950–958.
106. Rao SS, Hayek B, Summers RW. Functional chest pain of esophageal origin: hyperalgesia or motor dysfunction. *Am J Gastroenterol* 2001;96:2584–2589.
107. Eckardt VF, Stauf B, Bernhard G. Chest pain in achalasia: patient characteristics and clinical course. *Gastroenterology* 1999;116:1300–1304.
108. Cohen S, Fisher R, Lipshutz W, Turner R, Myers A, Schumacher R. The pathogenesis of esophageal dysfunction in scleroderma and Raynaud's disease. *J Clin Invest* 1972;51:2663–2668.
109. LeRoy EC, Black C, Fleischmajer R, Jablonska S, Krieg T, Medsger TA Jr, Rowell N, Wollheim F. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J Rheumatol* 1988;15:202–205.

Address requests for reprints to: Chair, Clinical Practice Committee, AGA National Office, c/o Membership Department, 4930 Del Ray Avenue, Bethesda, Maryland 20814. Fax: (301) 654-5920.

Supported by grants R01 DC00646 (to P.J.K.) and K23 DK062170-01 (to J.E.P.) from the Public Health Service.

The Clinical Practice Committee acknowledges the following individuals whose critiques of this review paper provided valuable guidance to the authors: Donald O. Castell, MD, Cecil H. Chally, MD, Ray E. Clouse, MD, and Richard H. Holloway, MD.