Impaired deglutitive EGJ relaxation in clinical esophageal manometry: a quantitative analysis of 400 patients and 75 controls

Sudip K. Ghosh, John E. Pandolfino, John Rice, John O. Clarke, Monika Kwiatek, and Peter J. Kahrilas

Department of Medicine, The Feinberg School of Medicine, Northwestern University, Chicago, Illinois

Submitted 6 June 2007; accepted in final form 8 August 2007

Ghosh SK, Pandolfino JE, Rice J, Clarke JO, Kwiatek M, Kahrilas PJ. Impaired deglutitive EGJ relaxation in clinical esophageal manometry: a quantitative analysis of 400 patients and 75 controls. Am J Physiol Gastrointest Liver Physiol 293: G878–G885, 2007. First published August 9, 2007; doi:10.1152/ajpgi.00252.2007.—Assessing deglutitive esophagogastric junction (EGJ) relaxation is an essential focus of clinical manometry. Our aim was to apply automated algorithmic analyses to high-resolution manometry (HRM) studies to ascertain the optimal method for discriminating normal from abnormal deglutitive EGJ relaxation. All 473 subjects (73 controls) were studied with a 36-channel solid-state HRM assembly during water swallows. Patients were classified as: 1) achalasia, 2) postfundoplication, 3) nonachalasia with normal deglutitive EGJ relaxation, or 4) functional obstruction (preserved peristalsis with incomplete EGJ relaxation). Automated computer programs assessed the adequacy of EGJ relaxation by using progressively complex analysis routines to compensate for esophageal shortening, crural diaphragm contraction, and catheter movement, all potential confounders. The single-sensor method of assessing EGJ relaxation had a sensitivity of only 52% for detecting achalasia. Of the automated HRM analysis paradigms tested, the 4-s integrated relaxation pressure using a cutoff of 15 mmHg performed optimally with 98% sensitivity and 96% specificity in the detection of achalasia. We also identified a heterogeneous group of 26 patients with functional EGJ obstruction attributed to variant achalasia and other diverse pathology. Although further clinical experience will ultimately judge, it is our expectation that applying rigorous methodology such as described herein to the analysis of HRM studies will improve the consistency in the interpretation of clinical manometry and prove useful in guiding clinical management.

esophageal manometry; lower esophageal sphincter; esophagogastric junction; achalasia

THE ASSESSMENT OF ESOPHAGOGASTRIC junction (EGJ) relaxation is a central focus of clinical esophageal manometry studies. Incomplete deglutitive EGJ relaxation is an essential feature in the manometric diagnosis of achalasia, and achalasia is not only the best-defined esophageal motor disorder (13) but also the one with the most specific treatments. These features impart great clinical relevance on the manometric detection of incomplete deglutitive EGJ relaxation. However, there is no accepted convention for defining incomplete deglutitive EGJ relaxation, and there are a number of potential confounding factors. Most notably, crural diaphragm contraction during respiration, deglutitive esophageal shortening, hiatal hernia, sphincter radial asymmetry, and recording-sensor movement relative to the EGJ can all have an impact on the quantification of deglutitive EGJ relaxation. Furthermore, although a variety of pressure-sensor technologies have been devised to circumvent some of these confounders (solid-state transducers, circumferentially sensitive transducers, Dentsleeve device, etc.), none is sufficiently robust to address them all (6, 9, 10, 12, 14).

A recent evolution in manometric methodology has been the introduction of solid-state high-resolution manometry (HRM), the basic concept being that by vastly increasing the number of high-fidelity manometric recording sites and decreasing the spacing between them, the intraluminal pressure environment of the esophagus and EGJ can be more completely defined, with minimal gaps between recording sites and, consequently, minimal movement-related artifact. This is of particular relevance to the assessment of deglutitive EGJ relaxation because of movement-related “pseudorelaxation” that occurs from a displacement of the recording sensor from the EGJ high-pressure zone, whether the movement be from deglutitive esophageal shortening or from the physical movement of the catheter during the course of the study. At the very least, purely on the technical grounds, solid-state HRM should improve the accuracy and consistency in quantifying EGJ relaxation (2, 3).

Despite its theoretical advantages, solid-state HRM is a relatively new technology, and there is no established convention to analyze deglutitive EGJ relaxation from HRM data. Partially filling this void, we recently performed a detailed analysis of EGJ relaxation by using HRM in 75 normal subjects (11). In that analysis, we summarized deglutitive relaxation characteristics by using standard measures as well as novel measures designed to take advantage of the higher sensor density and computer-analysis algorithms. However, the ultimate test of HRM is not in the characterization of normal subjects but in its application in the clinical domain. Thus the aim of the present study was to extend what we have learned thus far about deglutitive EGJ relaxation in normal subjects to HRM tracings of 400 consecutive patients with a spectrum of esophageal disorders. Our overarching goal was to develop a standardized analysis paradigm for esophageal HRM studies that optimally identifies impaired deglutitive EGJ relaxation.

METHODS

Patients. HRM studies done between February 2003 and July 2005 on 400 consecutive patients (248 male, ages 18–87) referred to the Northwestern Memorial Hospital manometry laboratory were analyzed. These patients presented with a diverse set of conditions to a tertiary care practice specializing in the management of esophageal disease. One hundred seventy-eight patients were undergoing evaluation for dysphagia, 146 for predominantly gastroesophageal reflux disease (GERD) symptoms (heartburn, regurgitation), 54 for chest pain, and 22 for miscellaneous complaints or follow-up. Thereafter, the patient’s medical records were analyzed along with their manom-

Address for reprint requests and other correspondence: S. K. Ghosh, Northwestern Univ., Feinberg School of Medicine, Division of Gastroenterology, Dept. of Medicine, 676 N. St., Clair St., Suite 1400, Chicago, IL 60611 (e-mail: s-ghosh@northwestern.edu).

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
etry tracing to establish the most likely pertinent diagnosis. Typical of a referral practice, some patients had already undergone treatment for their condition: 34 patients had prior fundoplication, and 38 patients had undergone treatment for achalasia (Botul injection, pneumatic dilation, Heller myotomy, or some combination of the three).

For the purposes of this analysis, patients were categorized into four major groups: 1) achalasia, 2) postfundoplication, 3) nonachalasia and normal deglutitive EGJ relaxation, and 4) functional obstruction (preserved peristalsis but abnormal deglutitive EGJ relaxation). The definition of achalasia required both impaired deglutitive EGJ relaxation and the absence of normal peristalsis. Normal or abnormal deglutitive EGJ relaxation was established by using the 95th percentile of normal established in the group of 73 control subjects for the relaxation measure being tested. Note that this caused some patients to be reassigned among groups 1 and 3 or 3 and 4 as criteria for incomplete EGJ relaxation changed. Achalasia patients who had already undergone successful treatment as determined by clinical response and/or timed barium swallow were analyzed separately. Only three patients were excluded from the final analysis: one for technical reasons (malfunctioning gastric sensor) and two with para-esophageal hernia that prevented intubation of the stomach. The study protocol was approved by the Northwestern University Institutional Review Board.

Clinical manometry protocol. A solid-state HRM assembly with 36 solid-state sensors spaced at 1-cm intervals (outer diameter 4.2 mm) was used (Sierra Scientific Instruments, Los Angeles, CA). The response characteristics of this device, calibration procedure, and poststudy thermal correction algorithm have been described in detail elsewhere (4, 11), but to summarize, each sensor is circumferentially sensitive, accurate to within 1 mmHg, capable of recording transient pressure changes in excess of 6,000 mmHg/s, zeroed to atmospheric pressure, and corrected for thermosensitive drift.

Studies were done in a supine position after at least a 6-h fast. The HRM assembly was passed transnasally and was positioned to record from the hypopharynx to the stomach with about three to five intragastric sensors. The catheter was fixed in place by taping it to the nose. The manometric protocol included a 5-min period to assess basal sphincter pressure and 10 5-ml water swallows. Manometric studies were acquired and stored by using ManoScan software (Sierra Scientific Instruments).

Manometric data were subsequently analyzed by using both ManoView analysis software and custom programs written in MATLAB (v. 7.3.0; The MathWorks, Natick, MA) after exporting them from ManoView in ASCII format. MATLAB was used because of its programming flexibility. Once written, MATLAB programs could be applied to systematically analyze each of the nearly 5,000 swallows in the manometric data set under analysis.

Characterization of deglutitive EGJ relaxation. Quantification of EGJ relaxation for the entire data set was done repetitively by using progressively more complex analysis routines. With each analysis paradigm, patients were reallocated among groups based on the findings, and the flaws of the deglutitive EGJ relaxation measure applied were analyzed on a case-by-case basis in the context of how it performed within the data set. Another metric of deglutitive EGJ relaxation for the entire data set was done repetitively by using the 95th percentile of normal established in the group of 73 control subjects for the relaxation measure being tested. Note that this caused some patients to be reassigned among groups 1 and 3 or 3 and 4 as criteria for incomplete EGJ relaxation changed. Achalasia patients who had already undergone successful treatment as determined by clinical response and/or timed barium swallow were analyzed separately. Only three patients were excluded from the final analysis: one for technical reasons (malfunctioning gastric sensor) and two with para-esophageal hernia that prevented intubation of the stomach. The study protocol was approved by the Northwestern University Institutional Review Board.

Clinical manometry protocol. A solid-state HRM assembly with 36 solid-state sensors spaced at 1-cm intervals (outer diameter 4.2 mm) was used (Sierra Scientific Instruments, Los Angeles, CA). The response characteristics of this device, calibration procedure, and poststudy thermal correction algorithm have been described in detail elsewhere (4, 11), but to summarize, each sensor is circumferentially sensitive, accurate to within 1 mmHg, capable of recording transient pressure changes in excess of 6,000 mmHg/s, zeroed to atmospheric pressure, and corrected for thermosensitive drift.

Studies were done in a supine position after at least a 6-h fast. The HRM assembly was passed transnasally and was positioned to record from the hypopharynx to the stomach with about three to five intragastric sensors. The catheter was fixed in place by taping it to the nose. The manometric protocol included a 5-min period to assess basal sphincter pressure and 10 5-ml water swallows. Manometric studies were acquired and stored by using ManoScan software (Sierra Scientific Instruments).

Manometric data were subsequently analyzed by using both ManoView analysis software and custom programs written in MATLAB (v. 7.3.0; The MathWorks, Natick, MA) after exporting them from ManoView in ASCII format. MATLAB was used because of its programming flexibility. Once written, MATLAB programs could be applied to systematically analyze each of the nearly 5,000 swallows in the manometric data set under analysis.

Characterization of deglutitive EGJ relaxation. Quantification of EGJ relaxation for the entire data set was done repetitively by using progressively more complex analysis routines. With each analysis paradigm, patients were reallocated among groups based on the findings, and the flaws of the deglutitive EGJ relaxation measure applied were analyzed on a case-by-case basis in the context of how it performed within the data set. Another metric of deglutitive EGJ relaxation analysis was then applied to, hopefully, overcome these flaws and the iterative process was repeated. In sequential order, deglutitive EGJ relaxation was measured by 1) a single manometric sensor centered in the EGJ high-pressure zone at the onset of the swallow, 2) the nadir relaxation pressure using the high-resolution data, 3) the optimal 3-s nadir eSleeve analysis as programmed in the current version of ManoView software (v. 1.4.1) and described by Clouse et al. (1), 4) the integrated relaxation resistance (IRR) as described in an earlier analysis of 75 normal subjects (11), 5) the 3-s integrated relaxation pressure (IRP), and 6) the IRP for 1- to 10-s intervals.

Determination of the nadir relaxation pressure, IRR, and IRP began by defining the temporal span and spatial limits of EGJ relaxation to be considered. On the basis of earlier work in normal subjects, the time period considered spanned from upper sphincter relaxation until the postperistaltic contraction at the EGJ or 10 s if no esophageal contraction occurred (Fig. 1A). The spatial limits of the EGJ subject to analysis were user defined, in most instances spanning from at least 2 cm to 6 cm, depending on extent of EGJ shortening after swallow.

Fig. 1. A: positioning of deglutitive relaxation window; pressure topography plot of a normal swallow with normal peristalsis. Onset of deglutitive relaxation window is defined by onset of upper esophageal sphincter (UES) relaxation, whereas offset is 10 s later. Spatial domain within which esophagogastric junction (EGJ) relaxation is assessed is user defined, spanning at least 6 cm, depending on extent of EGJ shortening after swallow. B: expanded view of relaxation window in A plotted as a series of spatial pressure-variation plots at top, with extracted maximal pressure values at bottom. For purposes of illustration, pressure values at top are sampled at only 2 Hz, whereas in actual computer algorithm (and for illustration at bottom), sampling rate was 35 Hz. Dots on each vertical spatial pressure-variation plot indicate locus of maximal pressure within relaxation window, along with its numerical value (mmHg).
Table 1. Measures of EGJ relaxation in normal subjects

<table>
<thead>
<tr>
<th>EGJ Relaxation Measure</th>
<th>Means ± SE</th>
<th>Median [Interquartile Range]</th>
<th>95th Percentile</th>
<th>Criterion of Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-sensor nadir, mmHg</td>
<td>1.1 ± 0.6</td>
<td>1.3 [1.4–2.7]</td>
<td>6.8</td>
<td>≥7 mmHg</td>
</tr>
<tr>
<td>HRM nadir, mmHg</td>
<td>3.9 ± 0.4</td>
<td>3.6 [1.9–5.8]</td>
<td>10.1</td>
<td>≥10 mmHg</td>
</tr>
<tr>
<td>3-s nadir eSleeve, mmHg</td>
<td>8.0 ± 0.4</td>
<td>7.5 [6.0–9.3]</td>
<td>14.7</td>
<td>≥15 mmHg</td>
</tr>
<tr>
<td>IRR, mmHg/s</td>
<td>1.3 ± 0.02</td>
<td>1.3 [1.0–2.1]</td>
<td>3.0</td>
<td>≥3 mmHg/s</td>
</tr>
<tr>
<td>1-s IRP, mmHg</td>
<td>6.7 ± 0.3</td>
<td>6.2 [5.0–7.7]</td>
<td>12.0</td>
<td>≥12 mmHg</td>
</tr>
<tr>
<td>2-s IRP, mmHg</td>
<td>7.2 ± 0.3</td>
<td>6.8 [5.5–8.2]</td>
<td>13.2</td>
<td>≥13 mmHg</td>
</tr>
<tr>
<td>3-s IRP, mmHg</td>
<td>7.8 ± 0.4</td>
<td>7.5 [5.8–9.0]</td>
<td>14.0</td>
<td>≥14 mmHg</td>
</tr>
<tr>
<td>4-s IRP, mmHg</td>
<td>8.6 ± 0.4</td>
<td>7.9 [6.4–10.0]</td>
<td>14.7</td>
<td>≥15 mmHg</td>
</tr>
<tr>
<td>5-s IRP, mmHg</td>
<td>9.5 ± 0.4</td>
<td>9.0 [6.8–11.3]</td>
<td>16.0</td>
<td>≥16 mmHg</td>
</tr>
<tr>
<td>6-s IRP, mmHg</td>
<td>10.7 ± 0.5</td>
<td>10.1 [7.5–12.6]</td>
<td>18.1</td>
<td>≥18 mmHg</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 73 patients. EGJ, esophagogastric junction; HRM, high-resolution manometry; IRR, integrated relaxation resistance; IRP, integrated relaxation pressure. See Fig. 2 for details of calculation.

**RESULTS**

Effect of EGJ relaxation measures on patient group distribution. Table 1 establishes the normal ranges for all of the EGJ relaxation measures under analysis, with the cutoff values for abnormal ranging from 7 to 18 mmHg. Note that the IRR is not...
directly comparable with the other measures because the unit of measure is in millimeters of mercury per second, incorporating both pressure and time. With every other measure analyzed, the relaxation period was specified by the definition of the measure.

Because deglutitive relaxation pressure was a major element of patient-group classification, the subtle differences in analysis methodology also had the effect of reallocating some patients between groups 1 and 3 (achalasia vs. nonachalasia diagnosis with normal EGJ relaxation) and groups 3 and 4 (nonachalasia diagnosis with normal EGJ relaxation vs. functional obstruction). The overall effect of analysis methodology on patient distribution among clinical categories is summarized in Table 2. Note that of the 62 achalasic patients established by all available clinical data, the sensitivity of detecting these from EGJ relaxation measures ranged from a low of 52% to a high of 98%. Also note that there were no false-positive achalasia diagnoses because of the stipulation that patients also exhibit aperistalsis. The one achalasia patient most consistently misclassified had an 3-s nadir eSleeve relaxation pressure of 15.1 mmHg and a 4-s IRP of 14.5 mmHg, clearly marginal by both measures. That patient had previously undergone a pneumatic dilation that was judged to be inadequately effective and subsequently improved greatly after a larger-caliber pneumatic dilation.

Nadir pressure vs. 3-s nadir eSleeve analysis. Table 3 contrasts the performance of the single-sensor nadir pressure method for assessing deglutitive EGJ relaxation with HRM nadir pressure measure. Note that there are 59 patients (15%) with discrepant findings. Examining the 31 patients characterized as having normal EGJ relaxation by the single-point sensor method and abnormal by the HRM nadir pressure measure, it becomes apparent that this discrepancy occurs in the setting of esophageal shortening with the phenomenon of pseudorelaxation (Fig. 3). On the other hand, there was no consistent explanation for the 28 patients with a normal HRM nadir relaxation pressure but an abnormal single-sensor value. Most commonly, these patients had single-sensor values in the 7- to 10-mmHg range, quantitatively agreeing with the HRM nadir values. In terms of the reliability of the two methods for detecting the set of achalasia patients, the HRM nadir method was clearly superior, improving the sensitivity of the measure from 52 to 87% with no change in specificity. This suggests that the pseudorelaxation effect can be a major confounder in assessing EGJ relaxation in achalasia patients.

Accepting the HRM nadir method as being the more robust of the two methods compared in Table 3, Table 4 contrasts its performance with the 3-s nadir eSleeve measure. Note that there are now 39 discrepant patients, most of whom were found to be abnormal only with the 3-s nadir eSleeve measure.
Table 4. Contingency table of agreement in identification of impaired EGJ relaxation between HRM nadir method and 3-s nadir eSleeve method

<table>
<thead>
<tr>
<th>HRM Nadir &lt; 10 mmHg</th>
<th>HRM Nadir ≥ 10 mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-s nadir eSleeve &lt; 15 mmHg</td>
<td>296</td>
</tr>
<tr>
<td>3-s nadir eSleeve ≥ 15 mmHg</td>
<td>32</td>
</tr>
</tbody>
</table>

Unweighted kappa statistic was 0.70 (95% confidence interval, 0.61–0.79), suggesting good agreement between methods.

Examining the 32 patients characterized as having normal EGJ relaxation by the single-point sensor method but abnormal by the 3-s nadir eSleeve, this discrepancy occurred mainly in the setting of abnormally brief deglutitive EGJ relaxation. The converse scenario of an abnormal HRM nadir measure but normal 3-s nadir eSleeve value occurred with nadir relaxation pressures in the 10- to 14-mmHg range, and none of these seven patients were ultimately judged to have a significant impairment of deglutitive EGJ relaxation. These observations suggest that brief periods of EGJ relaxation to nadir values within the normal range can be a confounder in assessing EGJ relaxation in a subset of achalasia patients and that the 3-s nadir eSleeve method improves both the sensitivity and specificity of detecting abnormal deglutitive relaxation relative to the HRM nadir pressure measure.

The 3-s nadir eSleeve vs. IRR. Table 5 contrasts the performance of the IRR method for assessing EGJ relaxation with the 3-s nadir eSleeve measure. Once again, although the kappa statistic demonstrates good agreement, there are 40 patients (10%) with discrepant results. Examining the groups with discrepant values fails to identify a clear winner with respect to analysis routine in this case. The dominant shortcoming of the 3-s nadir eSleeve method occurred in the setting of a rapid respiratory rate as illustrated in Fig. 4, such that there existed no contiguous 3-s period that could escape a confounding crural diaphragm contraction. On the other hand, the dominant problem with the IRR analysis was the somewhat unpredictable effect of varying relaxation duration. Unlike the case of control subjects, in whom the relaxation duration was relatively constant among individuals, this varied substantially in the patient group, ranging from a few seconds in patients with distal esophageal spasm to 10 s in the setting of aperistalsis. Thus, as illustrated in Fig. 5, a patient with a spastic nutcracker pattern in the distal esophagus had a shorter relaxation duration resulting in an abnormal IRR, whereas the 3-s nadir eSleeve was normal.

The above observations argue toward improving on both the 3-s nadir eSleeve measurement and the IRR by 1) removing the requirement that the scored deglutitive relaxation period be a completely contiguous time period and 2) standardizing the period of time during which relaxation is to be assessed.

The 3-s IRP vs. the 3-s nadir eSleeve method. The closest equivalent to the 3-s nadir eSleeve in terms of IRP (Fig. 2B) would be the 3-s value, making this the most appropriate initial comparator. Figure 6 illustrates a correlation analysis between these two measures. Clearly they are highly correlated, with an $r^2$ value of 0.90. However, there are still a few cases with a
for each measure, indicated by dashed lines. whereas those with normal eSleeve and abnormal IRP are shown as closed 3-s nadir eSleeve and normal by the 3-s IRP are shown as open diamonds, by both parameters are shown as closed circles. Subjects deemed abnormal by both parameters are shown as open circles, whereas subjects deemed abnormal these cardinal manometric abnormalities constitute the most impaired deglutitive EGJ relaxation. Thus patients with both of

Fig. 6. Correlation between 3-s IRP and 3-s nadir eSleeve measures in entire set of patients and controls. Correlation between both sets was excellent, with $r = 0.95$ and $r^2 = 0.90$. Subjects deemed to have normal EGJ relaxation by both parameters are shown as open circles, whereas subjects deemed abnormal by both parameters are shown as closed circles. Subjects deemed abnormal by 3-s nadir eSleeve and normal by the 3-s IRP are shown as open diamonds, whereas those with normal eSleeve and abnormal IRP are shown as closed diamonds. Most discrepant values are very close to threshold abnormal values for each measure, indicated by dashed lines.

discrepant result. Analysis of these cases suggests that the weakness of the 3-s nadir eSleeve analysis is the influence of the crural diaphragm, as shown in Fig. 4, and that this scenario did not confound the 3-s IRP metric. Illustrative of this, the 3-s IRP value for the example in Fig. 4 was 12.5 mmHg, well within the normal range. The net result of applying the 3-s IRP as opposed to the 3-s nadir eSleeve analysis to the entire data set was to reclassify six individuals from impaired to normal EGJ relaxation and one from normal to impaired. Thus, on balance, the 3-s IRP seemed the better measure, because the clinical data on the six reclassified individuals suggested that these were probably all false-positive 3-s nadir eSleeve values with none having a clinically significant impairment of deglutitive EGJ relaxation.

The optimal interval for IRP analysis. Consistent with the methodology detailed in Fig. 1, the longest possible IRP duration that could be assessed was 10 s. However, in most cases the actual limit is significantly shorter because the peristaltic sequence is a time-locked event that arrives at the EGJ before the 10-s cutoff. Thus one would anticipate that the specificity of the IRP measure would diminish as the period of analysis lengthened beyond 5–6 s. There is some suggestion of this in Table 2, because the IRP duration increased from 3 to 6 s with the number of false-positive individuals, with functional obstruction increased from 11 to 19. With respect to sensitivity, the most important objective was to identify achalasia patients. Figure 7 illustrates the sensitivity of detecting the achalasia population based solely on deglutitive EGJ relaxation-duration characteristics as the IRP duration was varied from 1 to 10 s. These analyses suggest that the optimal IRP period for analysis is 4 s, which also seemingly minimizes the number of misclassified patients in Table 2.

Patients with functional obstruction. Throughout this analysis, aperistalsis was required for a diagnosis of achalasia primarily because there is no gold standard for identifying impaired deglutitive EGJ relaxation. Thus patients with both of these cardinal manometric abnormalities constitute the most unequivocal diagnosis of achalasia. However, the restrictive definition may or may not be the actual case. An important observation in this study was that, regardless of the analysis paradigm used, there existed a subset of patients with intact peristalsis but abnormal deglutitive EGJ relaxation. Using all available clinical data (including all measures of deglutitive EGJ relaxation), we identified 18 such individuals with functional outflow obstruction at the EGJ. Figure 8A is an example of such an individual with a 4-s IRP of 33.5 mmHg and well-preserved peristalsis. This individual as well as the other five individuals with similar findings all had a dominant symptom of dysphagia and were diagnosed as achalasia variants; all were responsive to achalasia treatments. Figure 8B shows the postdilation manometry tracing from the same individual in Fig. 8A, now with normal EGJ relaxation. Of the remaining 12 individuals with functional obstruction, the final clinical diagnoses were variants of distal esophageal spasm ($n = 7$), eosinophilic esophagitis ($n = 3$), distal esophageal stricture ($n = 1$), and paraesophageal hernia ($n = 1$), thereby demonstrating the heterogeneity of this patient group.

Patients with fundoplication. Although a formal analysis of postfundoplication patients was not performed, we summarize here the salient EGJ relaxation measures for this patient group. Postfundoplication patients were characterized by the following EGJ relaxation characteristics: single-sensor nadir pressure, $5.7 \pm 0.8$ mmHg; HRM nadir pressure, $8.4 \pm 0.8$ mmHg; 3-s nadir eSleeve, $13.4 \pm 1.2$ mmHg; IRR, $2.0 \pm 0.2$ mmHg/s; 3-s IRP, $12.6 \pm 1.1$ mmHg; and 4-s IRP, $13.4 \pm 1.1$ mmHg. The end-expiratory EGJ pressure was $20 \pm 2$ mmHg.

DISCUSSION

Given that achalasia is, first and foremost, a disorder of lower esophageal sphincter (LES) relaxation, the detection of abnormal EGJ relaxation is a primary objective of clinical manometry. Hence, we performed a series of comprehensive automated analyses to establish the optimal criterion for detecting abnormal deglutitive EGJ relaxation based on a large group of patients with a broad spectrum of esophageal disorders and 73 control subjects. The major findings of the analysis

Fig. 7. Sensitivity analysis of IRP interval in detecting 62 achalasia patients. As IRP duration increases from 1 to 10 s, sensitivity declines because cutoff value for abnormal EGJ relaxation for each IRP duration is 95th percentile of control population; i.e., the specificity is held at 95%. Whereas 5-s IRP duration showed highest sensitivity, 4 s was chosen as optimum IRP duration because of lower number of false positives in functional obstruction patients (14 vs. 18; Table 2).

\[
\text{Sensitivity for identifying EGJ achalasia patient} \quad r^2 = 0.95\quad \text{and} \quad r = 0.90.
\]
were that, largely owing to the confounding effects of esophageal shortening and crural diaphragmatic contraction on quantifying deglutitive relaxation, the optimal measure was the average minimal integrated relaxation pressure for a 4-s interval. This single measure of deglutitive EGJ relaxation exhibited 98% sensitivity and 96% specificity for distinguishing well-defined achalasia patients from control subjects.

Because 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 EGJ relaxation. Before the current study, two studies (13, 15) using manometric methodology of adequate sophistication to control for the effect of esophageal shortening (a sleeve sensor and HRM with topographic analysis) had been published, both of which report findings quantitatively similar to the present study. Using a water-perfused Dentsleeve sensor, Shi et al. (13) reported the 95th percentile value for deglutitive EGJ relaxation of controls as 12 mmHg. In that series, a 12-mmHg relaxation pressure had a sensitivity and a positive predictive value of 92 and 88%, respectively, for a diagnosis of achalasia. In another study aimed at defining the optimal criteria for impaired EGJ relaxation, Staiano and Clouse (15) used HRM with topographic analysis, and similar accuracy was achieved by using a threshold value of 8–10 mmHg for the lowest mean residual pressure in a 3-s postdeglutitive interval, essentially a 3-s nadir eSleeve measure. The slight quantitative discrepancies between studies are likely explained by the enhanced recording fidelity and circumferential sensitivity of the device used in the current study.

The clinical utility of manometric studies, HRM or otherwise, is in demonstrating physiological abnormalities that correlate with symptoms and ultimately guide patient management. The classic example is achalasia. However, variant cases of achalasia will not necessarily demonstrate the classic manometric findings of both aperistalsis and impaired EGJ relaxation, making these criteria imperfectly sensitive (7, 8). Thus, although using the methods and thresholds defined in Table 1 will maximize diagnostic accuracy, manometry remains an imperfect tool for detecting achalasia because achalasia variants exist that can still confound the diagnosis. Illustrative of this was a report describing four achalasia variants in a retrospective study of 58 patients with idiopathic achalasia (5). 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 transient LES relaxations. Despite the use of a state-of-the-art technique, each of these achalasia variants had atypical features of either peristalsis or LES relaxation confounding their diagnosis. Nonetheless, in each case the patients were symptomatically improved following Heller myotomy, and histopathological analysis subsequently confirmed inflammation and destruction within the myenteric plexus. Similar to that series, the current series identified six patients with preserved peristalsis but impaired deglutitive EGJ relaxation that were given a clinical diagnosis of variant achalasia. However, to distinguish these patients from unequivocal achalasia and to also emphasize that cardinal abnormality in these patients was restricted to the EGJ, we classified them as functional obstruction. This diagnosis included a diverse set of disease states, including eosinophilic esophagitis, esophageal strictures, and paraesophageal hernia in this patient subtype. Although not illustrated in this paper, postfundoplication patients can also exhibit this pattern. It is important to note that these patients were eventually offered a course of treatment (dilation/surgery/glucocorticoids) that focused on eliminating the functional EGJ obstruction.

In summary, we have used a robust clinical experience of 400 consecutive patients and 73 control subjects to describe a novel methodology for the automated analysis of EGJ relaxation during solid-state esophageal HRM. We found the most accurate measure of deglutitive EGJ relaxation to be the 4-s IRP, essentially the average pressure during 4 s within the...
relaxation window with the most complete relaxation. This measure optimally compensated for the potential confounding influences of crural diaphragm contraction and deglutitive esophageal shortening. Although further clinical experience will ultimately be the judge, it is our expectation that applying rigorous methodology such as described herein to the analysis of HRM studies will improve the consistency in the interpretation of clinical manometry and will prove useful in guiding clinical management.

GRANTS
This work was supported by grants R01-DC-00646 (to P. J. Kahrilas) and K23-DK-62170-01 (J. E. Pandolfino) from the U.S. Public Health Service.

REFERENCES