CALL FOR PAPERS | Innovative and Emerging Technologies in GI Physiology and Disease

Adding a radial dimension to the assessment of esophagogastric junction relaxation: validation studies of the 3D-eSleeve

Frédéric Nicodème,1,2 John E. Pandolfino,1 Zhiyue Lin,1 Yinglian Xiao,2 Gabriela Escobar,1 and Peter J. Kahrilas1

1Department of Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Illinois; 2Department of Thoracic Surgery, Université de Montréal, Montréal, Quebec, Canada; and 3Department of Gastroenterology and Hepatology, First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China

Submitted 13 February 2012; accepted in final form 17 May 2012

Nicodème F, Pandolfino JE, Lin Z, Xiao Y, Escobar G, Kah- rilas PJ. Adding a radial dimension to the assessment of esophagogastric junction relaxation: validation studies of the 3D-eSleeve. Am J Physiol Gastrointest Liver Physiol 303: G275–G280, 2012. First published May 18, 2012; doi:10.1152/ajpgi.00063.2012.—High-resolution manometry (HRM) with esophageal pressure topography (EPT) circumvents many of the limitations of conventional manometry by utilizing enhanced spatial pressure resolution and data visualization. This has been particularly advantageous in the establishment of an objective quantitative measurement of esophagogastric junction (EGJ) relaxation, the integrated relaxation pressure (IRP), to distinguish between normal and abnormal EGJ relaxation (4). The IRP utilizes an electronic sleeve (eSleeve) paradigm to calculate the average pressure during the 4 s of most complete EGJ relaxation in the postdeglutitive period. This measurement was validated as a more accurate measure of EGJ relaxation than prior methods and currently has been adopted as a key measurement in the new HRM classification schemes for esophageal motor disorders (7).

Although the IRP is conceptually sound as a metric of EGJ relaxation, it is a very technology-sensitive measurement and normative values of the metric must be linked to the assembly with which they were derived. In work published thus far, standard HRM (model 360 HRM; Given Imaging, Los Angeles, CA) has been utilized. Enter 3D-HRM (Given Imaging), a technology that provides enhanced axial and radial pressure resolution developed specifically to overcome the shortcomings of standard HRM in addressing the radial asymmetry of the EGJ. Specifically, 3D-HRM preserves the individual pressure values of each radially dispersed sensor within the array. Recently published observations using this assembly suggest that the nadir pressure value at each axial level provide a higher fidelity recording of intraluminal pressure gradients and sphincter relaxation than do circumferentially averaged pressures on account of their being less influence of radial pressure asymmetries imparted by extrinsic structures (5, 6). Illustrative of this, comparison between spatial pressure variation plots and relaxation pressures derived from circumferentially averaged pressures suggest a persistent high pressure at the hiatal center during a period that flow is known to be occurring (Fig. 1), whereas this was not seen using the nadir radial pressure data.

Taken together, the above observations suggest that the 3D-HRM array using an analysis paradigm premised on finding the minimal radial pressure at each axial level (3D-eSleeve) should provide a representation of the luminal pressure gradient across the EGJ that is more relevant to predicting periods of transspincteric flow. Hence, we sought to test that hypothesis using barium transit on fluoroscopy as the comparator. We also sought to adapt the IRP metric to the 3D-HRM array using...
the 3D-eSleeve principle (3D-IRP) and compare normative values obtained with this new paradigm to standard IRP calculations.

MATERIALS AND METHODS

Subjects. Thirty-nine subjects were recruited during the two phases of the study. None of the subjects had a history of prior gastrointestinal surgery, significant medical disease, or were currently utilizing medications for upper gastrointestinal symptoms. All subjects underwent a brief interview and examination and gave written informed consent. Dysphagia was assessed using the Impaction Dysphagia Questionnaire (IDQ; maximal score: 50; 95th percentile cutoff in controls: 2). Reflux symptoms were measured using the Reflux Disease Questionnaire (RDQ; maximal score for heartburn or regurgitation: 20; normative cut-off: < 8). The study protocol was approved by the Northwestern University Institutional Review Board.

Manometry assemblies. The standard HRM assembly was a 4.2 mm outer diameter solid-state manometric assembly with 36 circumferential sensors spaced 1 cm apart (model 360 HRM; Given Imaging). Each level sensor averaged the pressure signals from the 12 radially dispersed sensors into a single circumferential pressure value. The data acquisition frequency was 25 Hz. All pressure measurements were referenced to atmospheric pressure.

The 3D-HRM assembly was a hybrid HRM assembly (model ManoScan 3D; Given Imaging), incorporating a 9.0-cm 3D-HRM segment into an otherwise standard HRM assembly (i.e., 28 standard sensing elements proximal to the 3D-HRM segment and 4 distally) (5, 6). The 3D segment was comprised of 12 rings of eight radially dispersed independent pressure sensors spaced 7.5 mm...
apart, for a total of 96 sensors. Consequently, the 3D segment could provide 12 radially averaged pressure signals similar to the standard HRM assembly or 96 independent pressure recordings across the EGJ during deglutitive relaxation. The data acquisition frequency was 100 Hz.

Prior to recording, both manometric assemblies were calibrated at 0 and 300 mmHg using the manufacturer’s calibration chamber. The technical specifications provided by the manufacturer were that the accuracy of the individual elements of the 3D array were ±1 mmHg for the pressure range of 0–50 mmHg and ±1.5 mmHg in the 50–100 mmHg range. The accuracy was tested using the manufacturer’s pressure chamber by applying pressure with a sphygmomanometer from 10 to 150 mmHg in increments of 10 mmHg. Each pressure was held for 5 s. After thermal compensation, the recorded pressures at each time and pressure increment were analyzed in Microsoft Excel.

**Phase I protocol: comparison of the IRP and 3D-IRP.** Twenty-five subjects underwent manometric evaluation with both the standard HRM assembly and the 3D-HRM assembly in randomized sequence within a 30-min time frame. Studies were performed in the supine position after a 6-h fast, and the subjects underwent a protocol that included ten 5-ml water swallows with each assembly. The assemblies were passed transnasally and positioned at the same location with at least three intragastric sensors in each case. During the 3D-HRM protocol, the swallow sequence was repeated twice: once with the 3D-HRM segment within the EGJ and once with the non-3D segment within the EGJ (Fig. 2).

**Phase II protocol: assessment of accuracy for determining bolus transit.** Fourteen subjects underwent simultaneous 3D-HRM evaluation and videofluoroscopy after a 6-h fast, using a C-arm fluoroscope (Easy Diagnostics; Phillips Medical Systems, Shelton, CT). Subjects were shielded below the umbilicus with a lead apron, along with a lead collar for thyroid protection. The 3D-HRM assembly was positioned as in phase I studies. The study protocol included recordings of two 5-ml barium swallows with the barium injected with a syringe into the mouth and swallowed as one bolus. The interval between swallows varied from 20 to 40 s. During the recording, the subjects were supine on a fluoroscopy table. Real-time fluoroscopic images were recorded through a video module (ManoScanV; Given Imaging).

**Fig. 3.** Snapshot of pressure recordings in the 3D segment of the 3D-HRM assembly within the esophagogastric junction (EGJ). **A**: standard eSleeve generated with 12 independent pressure recordings. **B**: 3D-eSleeve generated with 96 independent recordings (12 sensors levels × 8 radial sensors) utilizing the minimum radial pressure (3D-eSleeve) algorithm (notice the asymmetry with the 3D-eSleeve).

**Fig. 4.** Example of calculation of the flow permissive time (FPT) with the 3D-HRM assembly. FPT was defined as the time period, consecutive or not, when the esophageal pressure was higher than the EGJ eSleeve pressure, which in turn was higher than the gastric pressure. In this figure, standard FPT is present when esophageal pressure is greater than the standard eSleeve pressure, which in turn was greater than the gastric pressure. 3D-FPT is present when esophageal pressure is greater than the 3D-eSleeve pressure, which in turn was greater than the gastric pressure.
on the computer and synchronized with concurrent 3D-HRM recordings.

eSleeve and IRP analysis paradigms. As applied with standard HRM, the eSleeve is an analysis tool that detects the greatest pressure within a specified segment of the recording, serving as a means for quantifying residual pressure during sphincter relaxation. The eSleeve domain is typically 4–6 cm in length and can be modified during analysis so that it encompasses the EGJ high-pressure zone. The IRP is derived from the eSleeve recording during the 10-s period after the swallow. The analysis routine finds and averages the 4 s within that postdeglutitive window with the lowest eSleeve pressure. The median for the IRP, determined from a set of 75 normal subjects was 7.9 mmHg with the upper limit of normal being 15 mmHg (4).

The 3D-HRM assembly was used to calculate IRP in three different ways: 1) exactly analogous to with the standard HRM by positioning the 3D-HRM segment within the stomach and utilizing the standard segment (non-3D-segment) of the hybrid assembly, 2) analogous to with the standard HRM but using the 3D-HRM segment to compute it (Fig. 3A), and 3) using a novel 3D-IRP method (Fig. 3B). The 3D-IRP method isolated the minimal radial pressure at each axial sensor ring rather than using the average of the eight sensors with the caveat being that selected sensors in adjacent sensor rings must be in proximity to each other. This concept also was incorporated into the eSleeve paradigm as the 3D-eSleeve.

A beta version of ManoView software (Given Imaging) was used to calculate both IRP and 3D-IRP. MATLAB (version 2010b; The MathWorks, Natick, MA) programs were written to independently check these calculations and to assess the minimal number of radial sensors required to measure the 3D-IRP accurately. Simulations were done using eight sensors at 45 degrees, four sensors at 90 degrees (simulations with sensors 1, 3, 5, and 7 and sensors 2, 4, 6, and 8), two sensors at 180 degrees (sensors 1 and 5), and a single sensor of the assembly. For the cases of two and one single sensors, we arbitrarily selected the sensors, but their position within the EGJ was unknown and consequently random, depending on the orientation of the assembly when it was passed transnasally.

Comparing flow permissive time to bolus transit. A custom MATLAB program was written to calculate flow permissive time (FPT) as a derivative of: 1) the esophageal body pressure 2 cm proximal to the EGJ eSleeve domain, 2) intragastric pressure at least 2 cm distal to the EGJ eSleeve domain, 3) eSleeve pressure, and 4) 3D-eSleeve pressure (Fig. 4). The FPT was defined as the time during which esophageal pressure was greater than eSleeve pressure (3). The presence or absence of a bolus transit on the corresponding fluoroscopic images were coded with dichotomous values for each 0.1 s, and this was compared using a 2 x 2 contingency box with the FPT. The sensitivity and specificity of the FPT utilizing either the standard eSleeve or the 3D-eSleeve to predict bolus transit were compared. The

On the computer and synchronized with concurrent 3D-HRM recordings.

eSleeve and IRP analysis paradigms. As applied with standard HRM, the eSleeve is an analysis tool that detects the greatest pressure within a specified segment of the recording, serving as a means for quantifying residual pressure during sphincter relaxation. The eSleeve domain is typically 4–6 cm in length and can be modified during analysis so that it encompasses the EGJ high-pressure zone. The IRP is derived from the eSleeve recording during the 10-s period after the swallow. The analysis routine finds and averages the 4 s within that postdeglutitive window with the lowest eSleeve pressure. The median for the IRP, determined from a set of 75 normal subjects was 7.9 mmHg with the upper limit of normal being 15 mmHg (4).

The 3D-HRM assembly was used to calculate IRP in three different ways: 1) exactly analogous to with the standard HRM by positioning the 3D-HRM segment within the stomach and utilizing the standard segment (non-3D-segment) of the hybrid assembly, 2) analogous to with the standard HRM but using the 3D-HRM segment to compute it (Fig. 3A), and 3) using a novel 3D-IRP method (Fig. 3B). The 3D-IRP method isolated the minimal radial pressure at each axial sensor ring rather than using the average of the eight sensors with the caveat being that selected sensors in adjacent sensor rings must be in proximity to each other. This concept also was incorporated into the eSleeve paradigm as the 3D-eSleeve.

A beta version of ManoView software (Given Imaging) was used to calculate both IRP and 3D-IRP. MATLAB (version 2010b; The MathWorks, Natick, MA) programs were written to independently check these calculations and to assess the minimal number of radial sensors required to measure the 3D-IRP accurately. Simulations were done using eight sensors at 45 degrees, four sensors at 90 degrees (simulations with sensors 1, 3, 5, and 7 and sensors 2, 4, 6, and 8), two sensors at 180 degrees (sensors 1 and 5), and a single sensor of the assembly. For the cases of two and one single sensors, we arbitrarily selected the sensors, but their position within the EGJ was unknown and consequently random, depending on the orientation of the assembly when it was passed transnasally.

Comparing flow permissive time to bolus transit. A custom MATLAB program was written to calculate flow permissive time (FPT) as a derivative of: 1) the esophageal body pressure 2 cm proximal to the EGJ eSleeve domain, 2) intragastric pressure at least 2 cm distal to the EGJ eSleeve domain, 3) eSleeve pressure, and 4) 3D-eSleeve pressure (Fig. 4). The FPT was defined as the time during which esophageal pressure was greater than eSleeve pressure (3). The presence or absence of a bolus transit on the corresponding fluoroscopic images were coded with dichotomous values for each 0.1 s, and this was compared using a 2 x 2 contingency box with the FPT. The sensitivity and specificity of the FPT utilizing either the standard eSleeve or the 3D-eSleeve to predict bolus transit were compared. The

Table 1. Normal values for IRP and 3D-IRP (mmHg) using the standard HRM and 3D-HRM assemblies in 25 normal subjects, calculated using the β-ManoView software

<table>
<thead>
<tr>
<th>Assembly and Metric</th>
<th>Standard HRM</th>
<th>3D-HRM</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eSleeve Median, mmHg</td>
<td>5.3*</td>
<td></td>
</tr>
<tr>
<td>5th–95th percentile, mmHg</td>
<td>0.5–17.2</td>
<td>1.2–19.4</td>
</tr>
</tbody>
</table>

*Non-3D segment of the 3D-HRM assembly is similar to the standard assembly and composed of circumferential sensors spaced 1 cm apart. *Significant difference vs. 3D-IRP (P < 0.001) but no significant difference between these calculations. HRM, high-resolution manometry; IRP, integrated relaxation pressure; eSleeve, electronic sleeve.
determination of bolus transit and FPT were performed in a blinded fashion by two separate investigators.

Statistical analysis. In the phase I study, the values of the different measures of IRP were compared using the Kruskal-Wallis test, and the correlation between ManoView and MATLAB calculations were assessed by using the Pearson correlation coefficient. Data were summarized as median (5th-95th percentile), unless stated otherwise. A correlation between ManoView and MATLAB calculations were assessed by using the Pearson correlation coefficient. Data were summarized as median (5th-95th percentile), unless stated otherwise. A correlation between ManoView and MATLAB calculations were assessed by using the Pearson correlation coefficient. Data were summarized as median (5th-95th percentile), unless stated otherwise.

RESULTS

Subject demographics. Twenty-five subjects (17 female, ages 19–48) were recruited for the first phase of the study focused on comparing the measurement of IRP using the standard 360 degree-HRM assembly with the IRP obtained with the 3D-HRM assembly utilizing the maximum of the radial minimum pressure paradigm. Fourteen new subjects (6 female; ages 21–52) participated in the second phase of the study and underwent simultaneous 3D-HRM and videofluoroscopy to determine the efficacy of new 3D-HRM paradigms in predicting bolus transit. No subject had manometric evidence of hiatal hernia. Of the twenty-five subjects in phase I, 25 had a normal IDQ score and two had a borderline abnormal score of 8 and 9. Of the fourteen subjects in phase II, 13 had a normal IDQ score and one had a borderline abnormal RDQ score of 9. All subjects successfully completed the intended protocol.

Accuracy of the 3D-HRM array pressure sensors. The tested accuracy of the 3D-HRM array was such that each of the 96 sensing elements within it recorded the applied pressures in the range of 0–50 mmHg with an accuracy of ±0.98 mmHg after thermal compensation; the maximum standard deviation (SD) was 0.4 mmHg at greater pressures.

Figure 5 illustrates the mean, maximum, and minimum pressures after thermal compensation among the 96 sensing elements at a single time point of each 10 mmHg pressure increment for the calibration test. The maximum SD was 1.2 mmHg at greater pressures. It was not possible to accurately test the recording stability over time because we were unable to hold the pressure chamber pressurization constant to the required degree of accuracy. However, as the pressurization drifted slowly downward, all sensors responded in unison.

Comparison of IRP and 3D-IRP. The mean values and normative ranges of the IRP calculations for 25 control subjects are shown in Table 1 using the four different analysis protocols. There was no significant difference between IRPs calculated using the standard eSleeve, regardless of the HRM assembly. However, the 3D-IRP (calculated with the 3D-eSleeve) was significantly lower (P < 0.001) than all other calculations of IRP. These findings suggest that an appropriate upper limit of normal for the 3D-IRP is 12 mmHg.

The mean values and normative ranges of the IRP calculations for 25 control subjects are shown in Table 1 using the four different analysis protocols. There was no significant difference between IRPs calculated using the standard eSleeve, regardless of the HRM assembly. However, the 3D-IRP (calculated with the 3D-eSleeve) was significantly lower (P < 0.001) than all other calculations of IRP. These findings suggest that an appropriate upper limit of normal for the 3D-IRP is 12 mmHg.

We found a good correlation (r = 0.81, P < 0.001) between 3D-IRP average values calculated in MATLAB and those calculated in the β-ManoView software for the 25 subjects of the phase I (Fig. 6).

Minimal radial sensor density for 3D-IRP measurement. We used MATLAB simulations to compare the effect or reduced radial pressure resolution on calculated values of the 3D-IRP. Table 2 summarizes the comparison between using eight sensors at 45 degrees, four sensors at 90 degrees (2 different calculations), two sensors at 180 degrees, and a single sensor. The results suggest that the calculation using four sensors spaced 90 degrees slightly overestimated the value of the 3D-IRP, nevertheless with an excellent correlation with the eight-sensor analysis. Further reduction of the number of radial sensors was associated with a substantial drop in the correlation.

Using the 3D-IRP to calculate FPT. Twenty-eight swallows were analyzed using simultaneous 3D-HRM and videofluoroscopy. The median period of bolus transit assessed with videofluoroscopy was 3.3 s (0.3–4.9). The FPT was 2.1 s (0.4–4.0) with the eSleeve and 5.3 s (1.8–9.0) with the 3D-eSleeve. The presence or absence of FPT was compared with visualized bolus transit in videofluoroscopy during each tenth of a second for each swallow. The mean sensitivity and specificity of the eSleeve for predicting bolus transit were 0.55 and 0.85, respectively. In comparison, the mean sensitivity and specificity of the 3D-eSleeve were 0.78 and 0.88, respectively.

Table 2. MATLAB simulation of the 3D-IRP varying the radial resolution of the 3D assembly by selectively utilizing progressively fewer of the radial pressure sensors

<table>
<thead>
<tr>
<th>Number of sensors</th>
<th>8 (Nos. 1–3–5–7)</th>
<th>4 (Nos. 2–4–6–8)</th>
<th>2</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radial resolution, degrees</td>
<td>45</td>
<td>90</td>
<td>90</td>
<td>180</td>
</tr>
<tr>
<td>Median, mmHg</td>
<td>2.7</td>
<td>3.1</td>
<td>3.75</td>
<td>4.4</td>
</tr>
<tr>
<td>5th–95th percentile, mmHg</td>
<td>0.3–10.0</td>
<td>0.3–10.8</td>
<td>0.8–10.5</td>
<td>0.5–11.9</td>
</tr>
<tr>
<td>Correlation with the 8 sensors</td>
<td>R = 0.99</td>
<td>R = 0.98</td>
<td>R = 0.87</td>
<td>R = 0.44</td>
</tr>
<tr>
<td>P &lt; 0.001</td>
<td>P &lt; 0.001</td>
<td>P &lt; 0.001</td>
<td>P = 0.116</td>
<td></td>
</tr>
</tbody>
</table>

AJP-Gastrointest Liver Physiol • doi:10.1152/ajpgi.00063.2012 • www.ajpgi.org
DISCUSSION

A major advantage gained in the adoption of HRM with EPT over conventional manometry has been the establishment of an objective quantitative measurement of EGI relaxation, the IRP, to distinguish between normal and abnormal EGI relaxation (4). This study assessed whether or not a new 3D-HRM assembly could improve on this measurement with the 3D-eSleeve paradigm, an analysis premised on finding the axial maximum and radial minimum pressure at each sensor ring along the sleeve segment. The major findings of the study were that: 1) the upper limit of normal for the IRP was 12 mmHg (vs. 17 mmHg with the standard eSleeve) based on an analysis of 25 normal subjects, and 2) the residual sphincter pressure registered with the 3D-eSleeve was much more accurate in predicting intraluminal pressure gradients conducive to bolus flow (FPT) than the standard eSleeve as verified by concurrent fluoroscopy. These findings demonstrate a relevant difference between the two measurement paradigms and suggest that the 3D-eSleeve and 3D-IRP are the superior metrics to adopt for use with 3D-HRM.

The improved accuracy of the 3D-eSleeve should prove useful in the investigation and management of esophageal disorders ranging from achalasia to gastroesophageal reflux disease in which the assessment of EGI relaxation is a critical variable. Resolving the detail of the EGI high-pressure zone may allow one to discern whether resistance to flow at the EGI is due to impaired lower esophageal sphincter (LES) relaxation (8) or mechanical factors by differentiating unique features of radial symmetry and/or esophageal intrabolus pressure. The 3D analysis should also prove useful in gastroesophageal reflux disease studies as the same principles that affect antegrade flow will likely impact retrograde flow of gastric juice. There is also substantial interest in defining the intra-abdominal segment of the LES, and this assembly may have sufficient recording fidelity to make this measurement in real time, potentially improving upon measurements made during short interval pull-through evaluations of the LES.

One limitation of this study was that both the 3D-HRM and standard HRM assemblies studied were made by the same manufacturer (Given Imaging), making it impossible to generalize the findings more broadly. However, there is currently no way around this; there is only one solid-state 3D-HRM assembly currently available. In terms of the comparator, the 3D-HRM assembly could have been compared with an HRM assembly from a different manufacturer, but the other assemblies utilized in clinical HRM do not have published normative data for the IRP, which was the focal point of the present study. A comparison of 3D-HRM to a station pull-through with four radial recording sensors would be more valid; however, this technique is tedious, and it is difficult to see how problems related to movement artifact can be overcome.

Although not statistically significant, the IRP calculated with the standard eSleeve paradigm using the 3D-HRM segment was greater than that with the standard HRM assembly or the proximal segment of the hybrid 3D-HRM assembly. This may be related to the stiffness of the 3D-HRM segment, which could be reduced with lower sensor density. Our simulations suggested that four radial pressure orientations (90 degrees) may be sufficient to approximate the value of 3D-IRP, and this observation may have future implications in the design and development of the next generation of the 3D-HRM assemblies, even if the present study was not designed to validate these results.

In summary, we evaluated the feasibility of improving the measurement of IRP utilizing a novel 3D-HRM assembly and a novel 3D-eSleeve concept based on finding the axial maximum of the radial minimum pressures at each sensor ring along the sleeve segment. Our findings suggest that this approach is likely more accurate than standard HRM and other methods that utilize a radially averaged pressure within the EGI. Although we can only speculate on how much this will improve clinical management, 3D-HRM will certainly improve the accuracy of EGI relaxation measurements and this will certainly impact research endeavors focused on modeling EGI function during swallowing and reflux.

REFERENCES