Deglutitive upper esophageal sphincter relaxation: a study of 75 volunteer subjects using solid-state high-resolution manometry

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Ghosh, Sudip K., John E. Pandolfino, Qing Zhang, Andrew Jarosz, and Peter J. Kahrilas. Deglutitive upper esophageal sphincter relaxation: a study of 75 volunteer subjects using solid-state high-resolution manometry. Am J Physiol Gastrointest Liver Physiol 291: G525–G531, 2006. First published April 27, 2006; doi:10.1152/ajpgi.00081.2006.—This study aimed to use a novel high-resolution manometry (HRM) system to establish normative values for deglutitive upper esophageal sphincter (UES) relaxation. Seventy-five asymptomatic controls were studied. A solid-state HRM assembly with 36 circumferential sensors spaced 1 cm apart was positioned to record from the hypopharynx to the stomach. Subjects performed ten 5-ml water swallows and one each of 1-, 10-, and 20-ml volume swallows. Pressure profiles across the UES were analyzed using customized computational algorithms that measured 1) the relaxation interval (RI), 2) the median intrabolus pressure (mIBP) during the RI, and 3) the deglutitive sphincter resistance (DSR) defined as mIBP/RI. The automated analysis succeeded in confirming bolus volume modulation of both the RI and the mIBP with the mean RI ranging from 0.32 to 0.50 s and mIBP ranging from 5.93 to 13.80 mmHg for 1- and 20-ml swallows, respectively. DSR was relatively independent of bolus volume. Peak pharyngeal contraction during the return to the resting state postswallow was almost 300 mmHg, again independent of bolus volume. We performed a detailed analysis of deglutitive UES relaxation with a novel HRM system and customized software. The enhanced spatial resolution of HRM allows for the accurate, automated assessment of UES relaxation and intrabolus pressure characteristics, in both cases confirming the volume-dependent effects and absolute values of these parameters previously demonstrated by detailed analysis of concurrent manometry/fluoroscopy data. Normative values were established to aid in future clinical and investigative studies.

deglutitive sphincter resistance; relaxation interval; intrabolus pressure; mIBP

IT IS SOMEWHAT IRONIC that although the upper esophageal sphincter (UES) is the most accessible structure of the esophagus, it is in many ways the least well-understood. Several reflex pathways have been described linking the UES to the esophagus and pharynx (15, 20, 21, 23, 24) as well as between the esophagus and cricopharyngeal bar. However, the exception of belching-related dysfunction (14, 15), none of these observations have yet been linked to pathological conditions. With respect to pathological conditions, the only clear dysfunction of the UES relates to alterations in its response during swallowing, specifically impaired UES opening during swallowing and impaired relaxation during swallowing. Impaired opening, manifest as either stenosis with a cricopharyngeal bar or Zenker’s diverticulum (5, 8; 26), is a recognized cause of dysphagia. Impaired relaxation is probably less common but can be related to neurological dysfunction, best characterized in the case of Parkinson’s disease (1, 29). Thus, from a clinical perspective, the functional evaluation of the UES must, first and foremost, characterize deglutitive function.

The accurate manometric assessment of deglutitive UES relaxation faces unique technical challenges. Specifically, the sphincter moves discordantly with a manometric sensor during the course of the pharyngeal swallow, causing “pseudorelease” (13); its contractile characteristics are similar to those of the pharynx with a temporal contractile rate that exceeds the performance characteristics of perfused manometry systems (12), and it exhibits extreme circumferential asymmetry (13, 19, 27). Methodology has been described to overcome each of these complexities. The movement problem can be overcome with either a sleeve sensor (10, 12) or high-resolution manometry (HRM) in conjunction with fluoroscopy (17, 28). The rapid contractile response can be accurately recorded with solid-state manometry (3). The radial asymmetry can be controlled for with either a circumferentially sensitive sensor (3) or a flattened sleeve device that maintains a constant radial orientation (12). However, no manometric methodology has yet been described that overcomes all three of these formidable technical challenges. The aim of this study was to do just that. We utilized a new 36-channel solid-state HRM system to perform a detailed analysis of deglutitive UES function in normal individuals. Furthermore, with the goal of optimizing the clinical utility of the system, we developed new paradigms for the automated quantification of UES intrabolus pressure and relaxation duration during deglutition.

METHODS

Patients. Manometry studies were done on 75 asymptomatic subjects (40 male, ages 19–48 yr). Subjects consisted of volunteers recruited by advertisement or word of mouth with no history of gastrointestinal symptoms, upper gastrointestinal tract surgery, or significant medical condition. The study protocol was approved by the Northwestern University Institutional Review Board and informed consent was obtained from each subject.

HRM. A solid-state manometric assembly with 36 circumferential sensors spaced at 1 cm intervals (outer diameter, 4.2 mm) was used (Sierra Scientific Instruments, Los Angeles, CA). This device uses proprietary pressure transduction technology (TactArray) that allows each of the 36 pressure sensing elements to detect pressure over a length of 2.5 mm in each of 12 circumferentially dispersed sectors (Fig. 1). The sector pressures are then averaged to obtain a mean pressure measurement, making each of the 36 sensors a circumferential pressure detector with the extended frequency response characteristic of solid-state manometric systems. Before recording, the

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transducers were calibrated at 0 and 100 mmHg using externally applied pressure. The response characteristics of each sensing element were such that they could record pressure transients in excess of 6,000 mmHg/s and were accurate to within 1 mmHg of atmospheric pressure after thermal calibration correction (18). The data acquisition frequency was 35 Hz for each sensor.

HRM protocol. After a brief interview and examination to ensure the absence of gastrointestinal symptoms, subjects underwent transnasal placement of the manometric assembly. Studies were done in a supine position after at least a 6-h fast, and the manometric assembly was positioned to record from the hypopharynx to the stomach. Real-time pressure imaging during catheter intubation enabled accurate placement. 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, 10 water swallows of 5 ml, and 1 water swallow each of 1 (dry), 10, and 20 ml.

Manometry data analysis. Manometric data were initially analyzed using ManoView analysis software (Sierra Scientific Instruments). Further characterization of UES relaxation was performed with a computer program (MATLAB version 7.01; The MathWorks, Natick, MA) customized for processing binary manometric data into isocor- tour pressure plots and spatial pressure variation plots. This was done by first exporting the binary manometry data from ManoView in ASCII text format for processing and storage. These ASCII files were then reconverted into a double-precision binary format for use in MATLAB, and isocountour or spatial pressure variation plots were generated. In order for these plots to appear smooth (as opposed to notched), the dataset was enhanced both in the time dimension (between sampling times) and in the spatial dimension (between pressure recording sites). This interpolation was done using a piecewise cubic Hermite interpolation polynomial function in MATLAB implemented on a finely resolved rectilinear space-time grid to gen- erate intermediate data points, resulting in a virtual increase in the spatial data from 1 to 10 recording sites per cm and doubling the temporal sampling rate from 35 to 70 Hz (3, 9). Manometric data corresponding to the UES were isolated from the interpolated dataset using a computer program that defined the initiation of either UES relaxation or oral movement and the spatial limits of the UES high-pressure zone. UES spatial limits were defined by the transition to atmospheric pressure at the proximal margin and intrathoracic pressure at the distal margin. An example of the interpolated UES data is shown in Fig. 2A. Spatial pressure variation plots that allow a quantification of the pressure gradient across the UES during the period of deglutitive relaxation and bolus transport were also developed (Fig. 2B). The maximum pressures within the UES region during the deglutitive period were further derived from the spatial pressure variation plots (P_max; Fig. 2C). P_max consistently occurred after the passage of the bolus and, hence, was described as the peak pharyngeal contraction amplitude.

Deglutitive UES relaxation parameters. Deglutitive UES relaxation was characterized by minimal relaxation pressure, relaxation interval, median intrabolus pressure during the relaxation interval, and the deglutitive sphincter resistance (DSR). The computation of each of these was achieved using computer programs written in MATLAB. The programs analyzed the manometric data according to the algorithm detailed in Fig. 3. An isobaric contour analysis was done with progressively increasing pressure thresholds, and the cumulative UES relaxation time through the UES was tallied as a function of relaxation pressure (red line, Fig. 3E). An automated mathematical algorithm was then applied to objectively define the transition from intrabolus pressure at the end of the relaxation interval to sphincteric contraction. Central to this delineation is the recognition that the incremental increase in cumulative relaxation time in Fig. 3E diminishes as the dataset transitions from intrabolus pressure to sphincteric contractile pressure. A two-step algorithm was used to define the termination of the relaxation interval. First, the cumulative relaxation plot was fit to a smooth third-order curve (dotted line, Fig. 3E), and the point of inflexion (defined as the point at which the slope of the curve changed from positive to negative) was identified. Next, the cumulative relaxation time data (red line, Fig. 3E) before the point of inflexion was approximated with three continuous line segments optimized based on minimum residuals (green lines, Fig. 3, E and F). If the slope of the third line (Fig. 3, E and F) exceeded 20 mmHg per 0.1 s (Fig. 3F), then the beginning of the third line was selected as the transition point and the corresponding point on the cumulative relaxation plot taken as the termination of relaxation. However, if the pressure rise rate was less than 20 mmHg per 0.1 s (Fig. 3E), then the inflexion point defined by the smoothed curve (described earlier) was selected as the transition point and the corresponding point on the cumulative relaxation plot was taken as the termination of relaxation. The median intrabolus pressure (mIBP) was then derived from the cumulative relaxation plot as the isocountour pressure value at one half of the relaxation interval (Figs. 3, E and F). Finally, the DSR was calculated as the mIBP divided by the RI.

In every case, the results of the automated analyses were subsequently scrutinized on a case-by-case basis to ensure that the programmed algorithms had functioned properly. All pressure measurements were referenced to atmospheric pressure.

Statistical analysis. The mean, standard deviation, standard error, median, and interquartile ranges were calculated for all the paradigms developed above and are summarized in the ensuing graphics and tables. Differences across volumes were assessed using the Kruskal-Wallis test, and P values <0.05 were considered significant. In addition, a coefficient of variation (CV) analysis was used to assess the intrasubject variability for each paradigm. CV was calculated as the standard deviation divided by the mean for each subject and expressed as a percentage. The mean CV from all 75 subjects is
presented. CV was only calculated for the 5-ml volume swallows (10 swallows per subject).

RESULTS

Manometry was well-tolerated by all 75 subjects, and the studies were completed without technical problems. Spatial and temporal limits of deglutitive UES relaxation identified by the automated computer program were compared with manual observation in all 975 swallows, and no inconsistencies were observed in any swallow. Although the pattern of UES relaxation observed in Fig. 2 (with the sphincter moving 2 cm orad at the onset of the relaxation interval) was commonly observed, this was not universal. In many instances, minimal axial movement was evident, suggesting that sometimes the mano-
metric catheter and the sphincter elevated in synchrony. However, regardless of which pattern was evident, the analysis program consistently isolated the deglutitive data without being confounded by either sphincter or catheter movement.

UES relaxation parameters. As illustrated in Fig. 4, both the relaxation interval and the median intrabolus pressure during deglutitive relaxation increased with increasing swallow volume. The median RI from the 75 normal subjects was 0.31,
0.42, 0.44, and 0.48 s for the 1- (dry), 5-, 10-, and 20-ml swallows, respectively; all volumes were significantly different from each other ($P < 0.05$). Similarly, median intrabolus pressure increased from 5.93 to 7.58, 11.30, and 13.80 mmHg as the swallow volume was increased from 1 to 5, 10, and 20 ml, respectively. Interestingly, the minimum relaxation pressure also increased progressively from 3.18 to 5.42, 8.84, and 10.32 mmHg as the swallow volume was increased from 1 to 5, 10, and 20 ml, respectively. All permutations of differences in median intrabolus pressure and minimal relaxation pressure between volumes were significant ($P < 0.05$) except for the difference in median IBP between 1- and 5-ml swallows. Data values for all 975 swallows used to plot UES relaxation characteristics in Fig. 4 were as derived by the automated algorithm summarized in Fig. 3; in no case was it deemed necessary to introduce a manual correction.

The final parameter calculated to summarize deglutitive UES relaxation was DSR, designed to be indicative of resistance to flow across the sphincter during deglutitive UES relaxation but relatively independent of swallow volume. As illustrated in Fig. 5, DSR values were similar across the swallow volumes with only the 1- vs. 20-ml and 5- vs. 20-ml differences being significantly different. The average values with standard deviations and interquartile ranges for all parameters of UES relaxation are summarized in Table 1. Also included are data on the peak amplitude of the pharyngeal contraction, occurring at the end of the relaxation interval (Fig. 2C). Peak pharyngeal contraction values did not exhibit any volume dependency but did serve to highlight the recording characteristics of the manometric sensors with a typical temporal pressure gradient ($dP/dT$) exceeding 1,000 mmHg/s.

**Intrasubject variability.** The CV for each parameter of deglutitive UES relaxation is summarized in Table 2.
relaxation interval and the maximum pharyngeal contraction showed the minimum degree of variability (18.6% and 12.7%, respectively). On the contrary, the median IBP, minimum relaxation pressure, and DSR demonstrated a significant degree of variability within subjects. One explanation for this may be the low absolute magnitude of these measures that tends to make them appear great when expressed as a percent difference. Hence, the data in Table 2 are also expressed in the absolute magnitude of the CV for each measure in relevant units.

**DISCUSSION**

The major finding of this study was that a new solid-state HRM system, in conjunction with customized analysis software, could be applied to quantify the clinically relevant parameters of deglutitive UES relaxation previously obtainable only through the meticulous analysis of concurrent manometric and fluoroscopic studies (13). In addition, a dataset of normal values and ranges was developed from 75 normal volunteers, constrained to the age range (19–48 yr) of this study cohort, to serve as a reference for clinical manometry studies.

Two of the challenges faced in obtaining high-fidelity manometry recordings of deglutitive UES contractile activity are its extreme circumferential asymmetry (19) and rapid rate of contraction (3). These issues were easily accommodated with the HRM catheter we employed on the basis of its basic design with circumferential pressure sensitivity and extended frequency response. Earlier work by Castell and Castell (3) observed that temporal pressure gradients exceeding 450 mmHg/s are typical within the UES, and recording systems should be capable of matching this. The current manometry system readily identifies gradients of two to three times that magnitude.

The most vexing attribute of deglutitive UES relaxation pertains to movement of the sphincter as this can potentially introduce artifacts both at the onset and offset of the manometrically recorded relaxation interval. Indeed, most of the variability among published normative data on deglutitive UES relaxation is attributable to this methodological detail. We did our best to objectify this measurement by leveraging the inherent power of the HRM technique (which easily finds the onset of the relaxation interval) with a computational subroutine (Fig. 3) designed to optimally identify the transition from intrabolus pressure to sphincter contraction at the termination of the relaxation interval. The median RI values obtained using this algorithm exhibited volume dependency and ranged from 0.32 (1 ml) to 0.50 s (20 ml). These values compare quite favorably with those from an earlier publication (13) that precisely correlated videofluoroscopically monitored movement of the sphincter with relaxation interval recorded from radioopaque recording sites within the sphincter; the most comparable numbers from that publication (obtained with the sleeve sensor) ranged from 0.3 (dry swallow) to 0.51 s (20-ml swallow). The other major report of normative values for deglutitive UES relaxation was that by Castell and Castell (3), reporting a relaxation duration of 0.57 s for 5-ml swallows with a solid-state system. However, this difference is likely explained by the definition of relaxation employed in that work, onset at the point of departure from half the baseline and offset at the return to half-baseline pressure. That would be equivalent to extending the plots in Fig. 3, E and F, all the way up to half-baseline UES pressure and would necessarily increase the reported relaxation interval. More importantly, however, it would undermine the effort to quantify intrabolus pressure because it fails to draw a distinction between intrabolus pressure and the pressure of muscular contraction within the closed sphincter.

A major strength of the analysis algorithm detailed in Fig. 3 is that it objectifies the measurement of intrabolus pressure, likely one of the most clinically relevant attributes of deglutitive UES function (6, 9, 17). Using our algorithm, we present the summary statistics in Table 1 for median intrabolus pressure reported relaxation interval. More importantly, however, it would undermine the effort to quantify intrabolus pressure because it fails to draw a distinction between intrabolus pressure and the pressure of muscular contraction within the closed sphincter.

**Table 1. Statistical summary of upper esophageal sphincter relaxation parameters for 1-, 5-, 10-, and 20-ml swallows from 75 subjects**

<table>
<thead>
<tr>
<th>Swallow Volume, ml</th>
<th>Relaxation interval, s</th>
<th>Median IBP, mmHg</th>
<th>Minimum relaxation pressure, mmHg</th>
<th>DSR, mmHg/s</th>
<th>Peak pharyngeal contraction, mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.32±0.09 (0.26–0.39)</td>
<td>5.93±6.57 (1.5–10.25)</td>
<td>3.18±6.33 (–0.88–7.50)</td>
<td>22.60±28.70 (4.4–35.42)</td>
<td>265±64 (211–309)</td>
</tr>
<tr>
<td>5</td>
<td>0.41±0.09 (0.35–0.47)</td>
<td>7.58±4.40 (5.0–11.0)</td>
<td>5.42±4.53 (2.13–8.72)</td>
<td>20.46±15.33 (11.71–26.70)</td>
<td>285±75 (231–338)</td>
</tr>
<tr>
<td>10</td>
<td>0.45±0.13 (0.38–0.52)</td>
<td>11.30±4.67 (8.5–14.0)</td>
<td>8.84±4.84 (6.0–11.5)</td>
<td>31.40±32.50 (18.29–35.53)</td>
<td>292±74 (231–258)</td>
</tr>
<tr>
<td>20</td>
<td>0.50±0.11 (0.43–0.57)</td>
<td>13.80±4.76 (10.5–17.0)</td>
<td>10.32±5.31 (8.0–13.5)</td>
<td>33.25±19.49 (22.39–39.38)</td>
<td>297±91 (215–368)</td>
</tr>
</tbody>
</table>

Values are means ± SD (interquartile range) unless otherwise stated. IBP, intrabolus pressure; DSR, deglutitive sphincter resistance.

**Table 2. Coefficient of variation of upper esophageal sphincter relaxation parameters assessed from 10 5-ml swallows**

<table>
<thead>
<tr>
<th>Relaxation Interval</th>
<th>Median IBP</th>
<th>Minimum Relaxation Pressure</th>
<th>DSR</th>
<th>Peak Pharyngeal Contraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coefficient of variation, %</td>
<td>18.6</td>
<td>47.3</td>
<td>53.2</td>
<td>43.7</td>
</tr>
<tr>
<td>Mean SD</td>
<td>0.06 s</td>
<td>3.43 mmHg</td>
<td>2.8 mmHg</td>
<td>8.2 mmHg/s</td>
</tr>
</tbody>
</table>

Coefficients of variation are presented as percents, showing the SD normalized by the average representing the mean SD from 75 subjects. To illustrate the magnitude of variability within subjects in absolute units, the mean SD values are also shown.
REFERENCES

The algorithm always isolated the greatest pressure within the spatial domain of the UES, and, although negative pressure might occur at the inferior margin of the sphincter, these were usually negated by more positive proximal pressure.

Finally, a novel parameter developed in this analysis was DSR. The DSR was fairly uniform across different swallow volumes, thus acting as a normalizing parameter that removes volume dependent variations associated with relaxation duration and intrabolus pressure. This may prove useful in the clinical domain, because many patients with oropharyngeal dysphagia are unable to swallow larger bolus volumes safely (16). Hence, clinical studies performed only with lower volume boluses may be sufficient to assess the resistive properties of the sphincter and to guide therapeutic decisions.

In conclusion, we developed a set of novel parameters to objectively and reproducibly quantify normal deglutitive UES relaxation as measured from clinical HRM studies. These parameters are intended to provide a framework for clinical application of HRM to deglutitive UES function.

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