Original Article

Improving High-resolution Impedance Manometry Using Novel Viscous and Super-viscous Substrates in the Supine and Upright Positions: A Pilot Study

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Background/Aims

Swallows with viscous or solid boluses in different body positions alter esophageal manometry patterns. Limitations of previous studies include lack of standardized viscous substrates and the need for chewing prior to swallowing solid boluses. We hypothesize that high-resolution impedance manometry (HRiM) using standardized viscous and super-viscous swallows in supine and upright positions improves sensitivity for detecting esophageal motility abnormalities when compared with traditional saline swallows. To establish normative values for these novel substrates, we recruited healthy volunteers and performed HRiM.

Methods

Standardized viscous and super-viscous substrates were prepared using "Thick-It" food thickener and a rotational viscometer. All swallows were administered in 5-mL increments in both supine and upright positions. HRiM metrics and impedance (bolus transit) were calculated. We used a paired two-tailed t test to compare all metrics by position and substrate.

Results

The 5-g, 7-g, and 10-g substrates measured 5000, 36 200, and 64 700 mPa·sec, respectively. In 18 volunteers, we observed that the integrated relaxation pressure was lower when upright than when supine for all substrates ($P < 0.01$). The 10-g substrate significantly increased integrated relaxation pressure when compared to saline in the supine position ($P < 0.01$). Substrates and positions also affected distal contractile integral, distal latency, and impedance values.

Conclusions

We examined HRiM values using novel standardized viscous and super-viscous substrates in healthy subjects for both supine and upright positions. We found that viscosity and position affected HRiM Chicago metrics and have potential to increase the sensitivity of esophageal manometry.
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Key Words

Esophageal motility disorders; Manometry; Viscous substrates

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Introduction

High-resolution esophageal manometry (HRM) is the current gold standard test for diagnosing esophageal motility disorders.[1,2] The Chicago classification manometric diagnosis is based exclusively on HRM data derived from 10 liquid (normal saline) swallows performed in the supine position.[3-7] High-resolution impedance manometry (HRiM) catheters (Diversateck Healthcare Inc, Milwaukee, WI, USA) incorporate impedance and manometry sensors, providing information on esophageal peristaltic patterns and pressures as well as whether a bolus transit is complete. The protocol for HRiM testing consists of the patient swallowing ten 5-mL saline and ten 5-mL viscous solutions (Diversateck) in supine position.[8] Although viscous manometry and impedance values have not been integrated into the current Chicago classification, viscous impedance has been shown to be an important indicator of abnormal motility.[9] In a retrospective analysis, Clayton et al[9] showed that viscous impedance is the most sensitive indicator for detecting subtle esophageal function abnormalities independent of esophageal contractility.

Evaluating swallows with viscous or solid boluses in different body positions has been shown to alter esophageal manometry patterns and may increase sensitivity of motility studies.[9-13] Some patients with normal manometry studies with liquid swallows have been demonstrated to have diffuse esophageal spasm with solid food ingestion.[14] Furthermore, upright bread swallows can reveal motility abnormalities overlooked by supine saline swallows, particularly in patients with complaints of non-cardiac chest pain and gastroesophageal reflux disease.[10] While previous studies have used solid swallows, they lack standardization and their findings may be difficult to reproduce given the foods used. In addition, while upright swallowing may elicit subtle gastroesophageal junction outflow obstruction patterns on manometry, adjoining bolus transit abnormalities noted on impedance have not been properly evaluated.

We hypothesize that performing HRiM using standardized novel viscous and super-viscous swallows in the supine and upright positions will improve sensitivity for detecting esophageal motility abnormalities when compared with traditional saline swallows. Here, we report HRiM values obtained for these substrates in healthy volunteers.

Materials and Methods

The study was approved by the Institutional Review Board at the University of Maryland, Baltimore (IRB No. 00061276). After obtaining informed consent, a Diversateck HRiM catheter was placed into the esophagus and advanced to the lower esophageal sphincter in the standard fashion. Twenty-one healthy volunteers were recruited from the Baltimore VA Medical Center and the University of Maryland School of Medicine. Exclusion criteria included: (1) age less than 18 or older than 75 years, (2) body mass index > 35, (3) previously diagnosed gastroesophageal reflux disease or other esophageal motility abnormalities, (4) current use of acid suppression medications, (5) current use of any medications that affect gastrointestinal motility or perception, (6) dysphagia with either solids or liquids or both, and (7) pregnancy.

Viscous and super-viscous substrates were prepared by mixing 100 mL saline in a glass beaker with a stir bar with 5, 7, or 10 g of original gluten free "Thick-It" food thickener (Precision Foods, Inc, St. Louis, MO, USA) and then heating them up to the boiling point. The substrates were chosen based on viscosity and solubility. First, we determined that 10 grams are the maximal amount of "Thick-It" substrate that could make uniform viscous solution in 100 mL normal saline under boiling conditions. We then chose 5 grams as a second experimental group for comparison purposes. After we observed that 3 subjects exhibited oropharyngeal transfer difficulty with the 10-g super viscous solution, we decided to decrease the 10-g "Thick-It" amount. We tested with 9-g, 8-g, and 7-g solutions, and found that the 7-g solution was the easiest to swallow without oropharyngeal transfer difficulty. We measured the viscosity of each substrate with a digital rotational viscometer (Model NDJ-9s; Shanghai Longway Optical Instruments, Co, Ltd, Shanghai, China) in mPa·sec at room temperature. We either used these substrates on the same day or stored them in a 100-mL sterile container in a refrigerator for use within 1 week.

Volunteers first received either 10 (for the first 10 subjects) or 5 (for the last 8 subjects) supine saline swallows, followed by five 5-g swallows, then either five 7-g swallows or five 10-g swallows while supine. Subjects then received 5 saline (for only the last 8 subjects), five 5-g, and then either five 7-g or five 10-g swallows while upright. Because 3 subjects experienced oropharyngeal transfer difficulties with the super-viscous 10-g substrate, we replaced it with the 7-g substrate for all subjects after subject #13. A total of 21 volunteers enrolled and 3 were excluded (see Results section). There were a total of 140 supine saline swallows from 18 subjects; 90 supine 5-g swallows from 18 subjects; 40 supine 7-g swallows from 8 subjects; 45 supine 10-g swallows from 9 subjects; 40 upright saline swallows from 8 subjects; 90 upright 5-g swallows from 18 subjects; 40 upright 7-g swallows from 8 subjects and 45 upright 10-g swallows

from 9 subjects. Swallows were performed 30 seconds apart as per standard manometry testing protocol. Integrated relaxation pressure (IRP), distal contractile integral (DCI), distal latency (DL), peristaltic breaks (PB), and bolus transit were measured. We calculated medians, means, standard deviations, 5th, and 95th percentiles for each group. Impedance was analyzed using recovery of tracing to ≥ 50% of baseline at 5, 10, and 15 cm above the lower esophageal sphincter. Impedance results were noted as % of complete swallows/ total swallows. Paired two-tailed t test was used to compare all metrics by positions and substrates to supine saline swallows.

Results

The 5-g, 7-g, and 10-g viscous substrates measured 5000 mPa·sec at 21.6°C, 36 200 mPa·sec at 21.4°C, and 64 700 mPa·sec at 22°C, respectively. In comparison, Diversateck proprietary viscous solution measured 36 700 mPa·sec at 22°C. After testing 13 subjects, 3 subjects experienced oropharyngeal transfer difficulties with the super-viscous 10-g substrate, so it was replaced with the 7-g substrate.

Among the 21 volunteers enrolled, 3 were excluded (2 had significant double swallowing and 1 could not tolerate the manometry probe). The remaining 18 volunteers consisted of 10 men and 8 women with an average age of 35.3 ± 10.6 years (mean ± SD).

Average body mass index was 25.7 ± 3.9 kg/m^2 (mean ± SD). Eight were Caucasian, 8 were Asian American, and 2 were African American. No adverse event, including perforation, bleeding or aspiration, was reported by any of the study subjects after the procedures. Examples of HRiM studies are shown in Figure 1.

As shown in Table 1, IRP in the supine position was not significantly different when testing with 5-g or 7-g viscous solutions. However, IRP was higher when testing with super-viscous 10-g solution in comparison with saline ($P < 0.01$). When compared to testing with saline in the supine position, IRP was significantly lower in the upright position with all substrates including saline ($P < 0.01$), 5-g ($P < 0.01$), 7-g ($P < 0.01$), and 10-g ($P < 0.01$).

As shown in Table 2, DCI was significantly lower in the upright 5-g viscous ($P < 0.01$) and in upright 10-g super-viscous swallows ($P < 0.01$) than in the supine saline. No significant differences were noted in DCI when testing was performed using viscous and super-viscous substrates in the supine position, when compared to the traditional method (Table 2).

As shown in Table 3, DL was significantly higher in supine 5-g and 7-g viscous swallows than in supine saline swallows ($P < 0.01$). Upright saline and upright 7-g viscous swallows were also associated with higher DL than supine saline ($P < 0.05$).

With the exception of the supine 10-g super viscous substrate, PB was noted to be significantly higher in all substrates tested in the
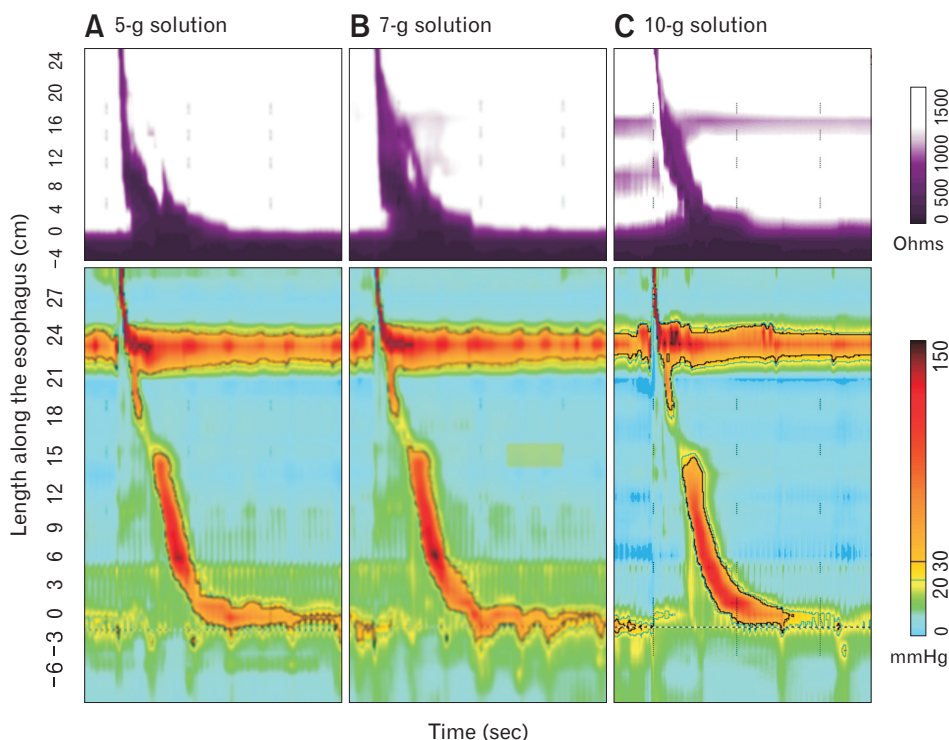
Figure 1. Examples of high-resolution impedance manometry studies using novel viscous and super-viscous solutions. Impedance and high-resolution manometry plots are shown in the top and bottom panels, respectively. (A) 5-g "Thick-It" solution. (B) 7-g "Thick-It" solution. (C) 10-g "Thick-It" solution.

Table 1. Integrated Relaxation Pressure Values

Position/substrate	Number of subjects	Number of swallows	IRP				
			Mean ± SD	Median	5%	95%	P-value
Supine saline	18	140	13.4 ± 5.0	13.0	5.0	22.0	
Supine 5 g	18	90	13.2 ± 4.8	13.5	4.5	21.0	0.581
Supine 7 g	8	40	12.8 ± 5.7	13.5	2.0	22.1	0.548
Supine 10 g	9	45	13.8 ± 4.7	14.0	7.0	21.0	< 0.01
Upright saline	8	40	7.5 ± 5.5	7.0	0.0	18.1	< 0.01
Upright 5 g	18	90	9.1 ± 5.8	8.0	2.0	20.6	< 0.01
Upright 7 g	8	40	9.8 ± 8.6	9.0	1.0	29.1	< 0.01
Upright 10 g	9	45	9.3 ± 5.3	9.0	3.0	15.0	< 0.01

IRP, integrated relaxation pressure.
P-values represent comparison with supine saline position with paired t tests.

Table 2. Distal Contractile Integral Values

Position/substrate	Number of subjects	Number of swallows	DCI				
			Mean ± SD	Median	5%	95%	P-value
Supine saline	18	140	1891 ± 1097	1742	654.6	3907.5	
Supine 5 g	18	90	1815 ± 1136	1928	378.5	3774.4	0.143
Supine 7 g	8	40	2020 ± 1717	2207	267.7	5364.7	0.444
Supine 10 g	9	45	1553 ± 1126	1426	68.2	3516.4	0.834
Upright saline	8	40	2519 ± 2829	2535	0.0	5311.3	0.980
Upright 5 g	18	90	1682 ± 1663	1401	22.8	5464.0	< 0.01
Upright 7 g	8	40	1721 ± 1378	1797	32.4	4697.1	0.070
Upright 10 g	9	45	1259 ± 1295	967	56.6	3055.4	< 0.01

DCI, distal contractile integral.
P-values represent comparison with supine saline position with paired t tests.

Table 3. Distal Latency Values

Position/substrate	Number of subjects	Number of swallows	DL				
			Mean ± SD	Median	5%	95%	P-value
Supine saline	18	140	6.8 ± 1.4	6.7	5.0	8.8	
Supine 5 g	18	90	7.5 ± 1.8	7.6	5.3	10.5	< 0.01
Supine 7 g	8	40	7.5 ± 2.3	7.8	5.3	10.9	< 0.01
Supine 10 g	9	45	7.0 ± 2.7	6.8	1.0	10.2	0.422
Upright saline	8	40	8.6 ± 4.8	7.1	5.2	16.4	< 0.05
Upright 5 g	18	90	7.8 ± 1.6	7.6	5.5	10.0	0.086
Upright 7 g	8	40	7.2 ± 2.8	7.6	0	10.5	< 0.05
Upright 10 g	9	45	8.1 ± 2.3	7.8	5.5	12.4	0.169

DL, distal latency.
*P-values represent comparison with supine saline position with paired t tests.

upright position ($P < 0.01$) (Table 4). PB in subjects tested with 5-g and 7-g substrates in the supine position was also higher than that for supine saline testing ($P < 0.01$).

In both the supine and upright positions, impedance was significantly lower with 5-g, 7-g, and 10-g substrates than with saline in the supine position (Table 5).

Table 4. Peristaltic Break Values

Position/substrate	Number of subjects	Number of swallows	PB					
			Mean ± SD	Median	5%	95%	P-value
Supine saline	18	140	0.8 ± 1.8	0.0	0	3.0	
Supine 5 g	18	90	1.4 ± 2.2	0.0	0	4.6	< 0.01
Supine 7 g	8	40	2.3 ± 3.1	0.5	0	10.1	< 0.01
Supine 10 g	9	45	1.6 ± 2.6	0.0	0	7.4	0.278
Upright saline	8	40	2.3 ± 2.8	0.5	0	7.5	< 0.01
Upright 5 g	18	90	2.8 ± 3.6	1.0	0	11.9	< 0.01
Upright 7 g	8	40	2.5 ± 2.7	0.0	0	7.1	< 0.01
Upright 10 g	9	45	4.8 ± 4.2	3.0	2.0	9.0	< 0.01

PB, peristaltic break.
P-values represent comparison with supine saline position with paired t tests.

Table 5. Impedance Values

Position/substrate	Number of subjects	Number of swallows	Impedance (%complete)	P-value
Supine saline	18	140	95%	
Supine 5 g	18	90	85%	< 0.01
Supine 7 g	8	40	88%	< 0.05
Supine 10 g	9	45	71%	< 0.01
Upright saline	8	40	88%	0.322
Upright 5 g	18	90	82%	< 0.05
Upright 7 g	8	40	88%	< 0.05
Upright 10 g	9	45	60%	< 0.01

P-values represent comparison with supine saline position with paired t tests.

Discussion

In our study, we examined HRiM values using standardized viscous and super-viscous substrates on 18 healthy subjects in supine and upright positions. These parameters were compared to the traditional method of testing with saline in the supine position. We found that position changes (upright vs supine) affected HRiM Chicago metrics. Testing while upright significantly reduced the IRP with saline and with all viscous substrates, including 5-g, 7-g, and 10-g. The DCI was also significantly lower when subjects were tested upright using the 5-g and the 10-g substrates when compared to the traditional method of using saline supine. These results are generally concordant with a study by Zhang et al[15] wherein 21 healthy volunteers and 25 patients received ten 5-mL liquid swallows and 5 "steamed bread" swallows in both supine and upright positions. Changing to upright position from supine position lowered DCI and IRP. When comparing liquid to solid swallows,

solid swallows exhibited more vigorous esophageal contractions (increased DCI).[15] Also, Xiao et al[16] performed HRiM on 75 healthy volunteers who received liquid swallows in both supine and upright positions and showed that DCI in upright position was dramatically reduced, when comparing to DCI in supine position.

In our cohort, we found that testing with the 10-g substrate in the supine position significantly increased the IRP when compared to saline in the supine position. Xiao et al[16] studied 148 patients with a range of complaints. All patients underwent 5 supine and 5 upright liquid swallows. Seventy-five of these 148 patients then underwent an upright "provocative swallow protocol" consisting of five 5-mL liquid swallows, two 10-mL liquid swallows, two 5-mL apple compote swallows, and 2 small marshmallow swallows. Interestingly, 11 patients demonstrated enhanced evidence of esophagogastric junction outflow obstruction with provocative swallows when conventional liquid swallows demonstrated normal or high normal range IRPs.[12] Three of these patients were treated with endoscopic measures to the lower esophageal sphincter with relief of dysphagia.[12] Therefore, in addition to evaluating bolus transit,[17] testing with different substrate viscosity may improve sensitivity of esophageal manometry. The ability to diagnose esophagogastric junction outflow obstruction is important as this diagnosis may be targeted therapeutically.

Compared to liquid swallows, solid food and viscous swallows are thought to be more sensitive to diagnose motility abnormalities. In 1990, Sears et al[11] noted that solid swallows increased the frequency of simultaneous/non-peristaltic swallows while upright positioning appeared to decrease esophageal peristaltic amplitudes. This was followed by an observation by Allen et al[14] in 1992 that sold food boluses could elicit simultaneous swallows in patients with non-cardiac chest pain.

In 2008, Bernhard et al[10] showed that high-resolution manometry patterns changed in patients with chest pain when upright bread swallows are administered compared to standard supine saline swallows. They concluded that evaluating bread swallows in the upright position reveals motility abnormalities overlooked by saline swallows alone. This study was performed before institution of the Chicago classification and thus used conventional manometry measurements to define motility changes despite using high-resolution equipment. Changing to upright position reduces DCI likely due to the aid of gravity. Using solid food boluses seems to increase DCI as the esophagus works to meet the demand of propagating a thicker bolus. Conflicting findings exist for IRP and DL, but most studies show a trend towards increased DL with solid or viscous swallows. In our study, compared with supine saline swallows, we observed significantly higher DL values in supine 5-g and 7-g viscous swallows ($P <$ 0.01), as well as higher PB values in subjects tested with 5-g and 7-g substrates in the supine position ($P < 0.01$). We did not see differences in IRP and DCI between supine viscous swallows and supine saline swallows.

There are several limitations to using solid boluses in HRiM studies. In an editorial titled "Use of solid boluses in high-resolution manometry," Wang and Sifrim[18] commented on inter-study discrepancies between the high-resolution metrics. These authors noted that during solid boluses the extent to which the patient chews the food and the proportion of the prescribed food swallowed may vary. Moreover, because these studies were conducted in China, the United States, and Europe, variations in patient demographics may have contributed to different results. The editorial concluded that the differences in previous studies "highlights the need for a standardized protocol and the potential need for localized normative value, as is the case in other gastrointestinal motility investigations."[18] No studies used the Diversateck's proprietary viscous substrate that is manufactured and standardized for their solid food swallow protocols. In our study, we developed novel standardized viscous and super-viscous substrates that are easy to make and are economical.

In addition to standardization difficulties between previous studies, impedance changes have been largely ignored. As impedance changes are the measure of true bolus transit through the esophagus (as opposed to manometric pressures generated during esophageal contractions), this parameter should be focused on as much as manometry.[19-22] Few studies incorporated impedance into their upright position analyses. A recent study by Park et al[23] evaluated the effect of upright saline swallows on impedance changes as well as their correlation to peristaltic breaks. They used patients who swallowed saline in an upright position and concluded that peristaltic breaks and incomplete bolus transit do correlate. However, the authors did not establish normal values and did not use viscous swallows. In our study, we showed that, in both supine and upright positions, impedance with our novel viscous and super-viscous solutions was significantly lower than with saline in the supine position.

Limitations of our study include the following: (1) small sample size. To establish normative values of these novel viscous and super-viscous solutions, larger healthy populations based on power calculations will be required; (2) 3 subjects experienced oropharyngeal transfer difficulties on the 10-g super-viscous substrate, therefore, for studies using 10-g substrates, patients will need to be taught proper swallowing techniques to ensure appropriate oropharyngeal transfer prior to initiation of swallows.

In conclusion, we developed novel standardized viscous and super-viscous substrates in a pilot study that are both safe and widely available, and demonstrated the feasibility of using these substrates in HRiM studies. In future studies, we plan to establish normative HRiM values using a larger number of healthy subjects and also evaluate patients with motility disorders and determine whether these viscous and super-viscous substrates improve either diagnostic sensitivity and/or treatment outcomes.

Conflicts of interest: None.

Author contributions: Erik B Person, Uni Wong, and Guofeng Xie performed the research; Guofeng Xie and Erik B Person designed the study; Donald O Castell, Erik von Rosenvinge, and Jean-Pierre Raufman contributed essential tools and to regulatory approvals; Uni Wong analyzed the data; and Guofeng Xie wrote the initial draft and all authors contributed to and approved the final paper.

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