# Pharyngo-Esophageal Modulatory Swallow Responses to Bolus Volume and Viscosity Across Time

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**Objectives/Hypothesis:** Modulation of the pharyngeal swallow to bolus volume and viscosity is important for safe swallowing and is commonly studied using high-resolution pharyngeal manometry (HRPM). Use of unidirectional pressure sensor technology may, however, introduce variability in swallow measures and a fixed bolus administration protocol may induce time and order effects. We aimed to overcome these limitations and to investigate the effect of time by repeating randomized measurements using circumferential pressure sensor technology.

Study Design: Sub-set analysis of data from the placebo arm of a randomized, repeated measures trial.

**Methods:** HRPM with impedance was recorded using a solid-state catheter with 36 circumferential pressure sensors and 18 impedance segments straddling from hypopharynx to stomach. Testing included triplicates of 5, 10, and 20 ml thin liquid and 10 ml thick liquid boluses, the order of the thin liquid boluses was randomized. The swallow challenges were repeated approximately 10 minutes after finishing the baseline measurement.

**Results:** We included 19 healthy adults (10/9 male/female; age 24.5  $\pm$  4.1 year). Intrabolus pressure, all upper esophageal sphincter (UES) opening and relaxation metrics, and flow timing metrics increased with larger volumes. A thicker viscosity decreased UES relaxation time, UES basal pressure, and flow timing metrics, whereas UES opening extent increased. Pre-swallow UES basal pressure and post-swallow UES contractile integral decreased over time.

**Conclusion:** Using circumferential pressure sensor technology, the effects of volume and viscosity were largely consistent with previous reports. UES contractile pressures reduced over time. The growing body of literature offers a benchmark for recognizing aberrant pharyngo-esophageal motor responses.

**Key Words:** Deglutition, dysphagia, high-resolution manometry, impedance, pharynx. **Level of Evidence:** 3

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## INTRODUCTION

Oropharyngeal swallowing is a highly complex process requiring adequate neuro-regulation and modulation to safely transfer the bolus from the mouth to the esophagus.<sup>1</sup> Afferent sensory information from the mouth and

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oropharynx is important for accommodation of the swallow motor response to a specific bolus.<sup>2–7</sup> Bolus properties like volume, viscosity, taste, and temperature serve as peripheral sensory input to the brainstem.<sup>1,4,8,9</sup> This information is integrated with input from cortical areas<sup>1,9</sup> and may influence the central pattern generator neurons within the brainstem, resulting in a motor output of the swallow response adjusted for sensory feedback.<sup>1,3,9</sup>

The effect of modification of bolus textures and volumes is commonly used in dysphagia management and is an established compensatory technique.<sup>10,11</sup> Thickened liquids increase the safety of swallowing by reducing the prevalence of penetration and aspiration, although the prevalence of postswallow residue may increase.<sup>12</sup> Additionally, it has been shown that sensory stimulating liquids (ie, sour, cold, and carbonated liquids, and capsaicinoids) induce biomechanical changes of the swallow<sup>8</sup> and increase swallow safety<sup>13</sup> in patients with dysphagia. Sensory stimulation may therefore also be of importance as a dysphagia intervention.<sup>8,13</sup>

Some studies show that patients with oropharyngeal dysphagia or aspiration have an altered response to changes in bolus volume and viscosity.<sup>4,14–16</sup> For instance, a decreased pharyngeal delay with increasing bolus volumes was found in stroke patients, with most of them having mild swallow abnormalities, but not in healthy subjects.<sup>4</sup> Another study demonstrated an increased difference in maximal velopharyngeal pressure between thin

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and thick liquids in patients who aspirated as compared to nonaspirating patients and patients without dysphagia.<sup>15</sup> This may suggest that patients with dysphagia have an altered or decreased ability to modulate their swallow response, potentially increasing the likelihood for bolus penetration or aspiration.

The motor output of the swallow response, or the biomechanics of swallowing, is increasingly studied using high-resolution pharyngeal manometry (HRPM).<sup>17</sup> Integration of high-resolution manometry with impedance measurement enables assessment of bolus flow patterns in conjunction with pressure events.<sup>18,19</sup> Recently, a working group established recommendations for standardizing measurement protocols and constructed a standard outcome set of diagnostic HRPM metrics via a Delphi consensus process.<sup>17</sup>

Several studies characterized the modulatory response of the pharyngeal swallow to different bolus volumes and/or viscosities using HRPM.<sup>15,20–34</sup> These may serve as reference for assessment of swallow modulation in patients with dysphagia. A recent study demonstrated modulatory effects to a wide range of volumes and viscosities using unidirectional HRPM with impedance in a large population of healthy participants.<sup>34</sup> This study had acknowledged limitations, particularly the use of unidirectional sensor technologies, the potential effect of topical anesthesia and, as with many studies in the past, they did not randomize the protocol of bolus administration allowing for the potential for their data to be influenced by time and order effects.

Because it is important to confirm and expand upon previous findings, we aimed to confirm the physiologic swallow responses to bolus volume and viscosity using circumferential pressure sensing technology with impedance and a randomized protocol for bolus administration. Furthermore, we sought to examine the effect of time by repeating these measurements during a single session.

## MATERIALS AND METHODS

## Study Design and Population

We studied the swallow modulatory response by performing a sub-set analysis of measurements from 20 healthy subjects (age range 18-40) enrolled in a randomized placebo-controlled trial investigating opioid drug efficacy (ClinicalTrials.gov registration number: NCT03283020).<sup>35</sup> The study was conducted at the Department of Anesthesiology and Intensive Care of the Örebro University Hospital, Sweden. The protocol was approved by the Central Ethics Review Board in Uppsala (Dnr 2017/270; 12/07/2017), Sweden, and was in accordance with the Declaration of Helsinki. The data from the placebo arm are reported here. Exclusion criteria were: anamnesis of swallow problems; known or history of gastrointestinal, cardiac, pulmonary or neurological disease; medication that could affect the upper gastrointestinal tract, larynx or lower airway; allergies to remifentanil, fentanyl analogs or methylnaltrexone; pregnancy or breast feeding; body mass index (BMI) > 30; smoking; participation in a trial during the previous 12 months where an opioid was used; participation in any other trial in the last 30 days or in a trial where follow-up was not completed. All subjects gave written informed consent before inclusion.

#### **Data Acquisition**

Manometry data with impedance was collected using the ManoScan ESO high-resolution manometry system (Medtronic, Minneapolis, Minnesota). The 4.2-mm-diameter solid-state pressure and impedance catheter was used, incorporating 36 1-cmspaced circumferential pressure sensors and 18 adjoining impedance segments each of 2-cm length. The catheter was calibrated before use with each participant according to manufacturer's specifications. Data were recorded from hypopharynx to stomach at a sampling rate of 50 Hz.

## Study Protocol

Participants were instructed to fast from food for 6 hours and clear drinks for 2 hours prior to the procedure. The HRM with impedance catheter was introduced trans-nasally without topical anesthesia. After a 5-minute accommodation period, the baseline measurement (time point 1) was performed. Participants were tested in a 30° recumbent position. Testing included triplicate swallow challenges across four liquid bolus conditions: 5, 10, and 20 ml thin fluid (International Dysphagia Diet Standardization Initiative [IDDSI] 0) and 10 ml extremely thick fluid (IDDSI 4) according to the IDDSI protocols.<sup>36</sup> The test bolus was prepared using the Standardized Bolus Medium (SBMkit) product (Trisco Foods Pty Ltd, Australia), comprising sodium chloride (NaCl) concentrate solution and a separate gum-based thickener (Precise Thick'N Instant) added to tap water. The order of administration of the thin liquid swallows was randomized, the 10 ml extremely thick bolus was always last in order. Boluses were administered via a syringe and participants were instructed to swallow the bolus in one attempt. Approximately 10 minutes after completion of the baseline measurement, the swallow challenges were repeated (time point 2).

## **Data Analysis**

Pressure and impedance data were analyzed using the online analysis platform Swallow Gateway for both pharyngeal and esophageal HRM data (swallowgateway.com, Flinders University, Adelaide, Australia). After exporting the study data as an ASCII file and uploading it to the web-application, spatiotemporal landmarks were manually selected and HRPM metrics were automatically derived. Analysis details and reliability have been previously described.<sup>37</sup> Multiple swallow events (< 5 seconds apart) were excluded from analysis.

Pressures recorded for the meso- and velo-pharyngeal regions were not consistently captured in all cases, thus the metrics presented in this study comprise those from the core outcomes set<sup>17</sup> that could be calculated from the acquired pressure impedance tracings which straddled from the hypopharynx to the proximal esophagus, see Figure 1. These were: hypopharyngeal contractile integral (HPCI), hypopharyngeal intrabolus pressure (IBP), upper esophageal sphincter (UES) integrated relaxation pressure (UES IRP), UES relaxation time (UES RT) and UES maximum admittance (UES Max Ad). Additionally, we determined pre-swallow UES basal pressure (UES BP), post-swallow UES contractile integral (UESCI) and peak pressure (UES PP), proximal esophageal contractile integral (PCIes), pharyngeal distension-contraction latency (DCL), bolus presence time (BPT) and the Swallow Risk Index (SRI) (see Table I for definitions).

## Statistical Analysis

Continuous baseline variables were summarized as mean  $\pm$  standard deviation. Participant averages for HRPM metrics derived for each bolus condition and time point were statistically compared using the mixed effects linear regression model



Fig. 1. A pressure topography tracing of a swallow from hypopharynx to proximal esophagus with metrics incorporated in the figure, corresponding to the definitions given in Table I. The graphs represent pressure (black) and admittance (pink) curves at the level of the hypopharynx (upper graph) and the upper esophageal sphincter (lower graph). [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

(IBM SPSS Statistics for Windows, version 25.0; IBM Corp, Armonk, New York). We started with the full interaction model to investigate whether the effect of bolus changed over the different time points. We removed the interaction if not statistically significant. In the first instance, models were fitted on the untransformed HRPM metrics. Residuals were visually inspected for homoscedasticity and normality. Metrics with right skewed residuals were log-transformed (natural logarithm). Models were then refitted on the transformed data. Data were expressed as estimated means (95% confidence interval [95% CI) or estimated back-transformed means (95% CI) for the log-transformed metrics. Additionally, estimated mean differences (95% CI) are reported, with estimated mean log differences (95% CI) for the log-transformed metrics. Bonferroni correction was applied to account for multiple comparisons. *P*-values < .05 were considered statistically significant.

## RESULTS

One participant did not complete the protocol. Therefore, swallow modulation data are reported from 19 (10/9  $\,$ 

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TABLE I.

The Core Outcomes Set Metrics and Additional Metrics Determined With Pharyngeal High-Resolution Impedance Manometry Subdivided into Metric Classes.

Metric Class	Metric	Acronym (Units)	Definition					
Core outcomes set metrics								
Hypopharyngeal contractility	Hypopharyngeal contractile integral	HPCI (mmHg⋅cm⋅sec)	The integral of pressures within the hypopharyngeal region indicating contractile vigor of the hypopharynx					
Hypopharyngeal intrabolus distension pressure	Intrabolus pressure	IBP (mmHg)	The pressure at the time of maximum hypopharyngeal distension (maximum admittance) measured at 1 cm superior to the UES apogee					
UES relaxation and opening metrics	UES integrated relaxation pressure	UES IRP (mmHg)	The extent of UES relaxation defined as the median of the lowest pressures in a non- consecutive window of 0.25 sec					
	UES relaxation time	UES RT (sec)	Duration of UES relaxation defined as the interval when pressure is < 50% of baseline or < 35 mmHg (the lowest)					
	UES maximum admittance	UES Max Ad (mS)	UES opening extent measured as the maximum UES admittance (inverse of impedance) during bolus flow in millisiemens					
Additional metrics								
UES contractile metrics	UES basal pressure	UES BP (mmHg)	Mean of UES axial maximum pressures preceding UES relaxation					
	UES contractile integral	UESCI (mmHg⋅cm⋅sec)	The integral of pressures of the UES post-swallow, indicating UES contractile vigor					
	UES peak pressure	UES PP (mmHg)	UES peak pressure measured after pharyngeal contraction					
Proximal esophageal contractile metric	Proximal esophageal contractile integral	PCles (mmHg⋅cm⋅sec)	The integral of pressures > 20 mmHg within the proximal esophagus region, indicating contractile vigor of the proximal esophagus					
Flow timing metrics	Pharyngeal distension-contraction latency	DCL (sec)	The average time from maximum pharyngeal bolus distension to peak pressure, indicating how well the bolus is propelled ahead of the pharyngeal stripping wave					
	Bolus presence time	BPT (sec)	The bolus dwell time in the hypopharynx					
Global swallow risk index	Swallow Risk Index	SRI	Composite score combining 4 HRPM metrics, indicating global swallowing dysfunction and risk for aspiration					

BPT = bolus presence time; DCL = distension-contraction latency; HPCI = hypopharyngeal contractile integral; HRPM = high-resolution pharyngeal manometry; IBP = hypopharyngeal intrabolus pressure; PCIes = proximal esophageal contractile integral; SRI = Swallow Risk Index; UES = upper esophageal sphincter; UES BP = UES basal pressure; UES IRP = UES integrated relaxation pressure; UES Max Ad = UES maximum admittance; UES PP = UES peak pressure; UES RT = UES relaxation time; UESCI = UES contractile integral.

male/female; age 24.5  $\pm$  4.1 year; BMI 22.9  $\pm$  1.9 kg/m<sup>2</sup>). A total of 450 swallows were analyzed. The mean time from the start of the baseline measurement to the start of the second swallow series was 15 minutes:25 seconds  $\pm$  1 minute:48 seconds. Figure 2A–D shows the effect of bolus volume and viscosity on each metric and Table II displays the main effect and the pairwise comparisons for volume and viscosity. None of the parameters showed significant time—bolus type interaction.

## Hypopharyngeal Contractility

A numerical increase in HPCI was observed with larger volumes (main effect P = .055). Viscosity did not affect hypopharyngeal contractility, see Figure 2A.

## Hypopharyngeal Intrabolus Pressure

IBP significantly increased with larger bolus volumes (main effect P < .001). Pairwise comparisons

showed a significant increase in IBP with larger volumes across two volume combinations (5 vs. 10 ml and 5 vs. 20 ml IDDSI 0), see Table II. Interestingly, a thicker viscosity did not increase IBP (Fig. 2B).

## **UES Relaxation and Opening Metrics**

Bolus volume augmented all UES relaxation and opening metrics, whereas viscosity only affected UES RT and UES Max Ad (main effects of all UES relaxation and opening metrics: P < .001), see Figure 2B,D. Like IBP, UES IRP showed a significant increase with larger volumes for 5 versus 10 ml and 5 versus 20 ml and did not show an effect with increased viscosity (for pairwise comparisons see Table II). As expected, UES RT was significantly longer with larger volumes and shorter with thicker fluids (Fig. 2D), and UES opening extent (UES Max Ad) significantly increased with both volume and viscosity (Fig. 2B).



Fig. 2. A–D, Effects of volume and viscosity displayed by estimated mean values with 95% confidence interval (95% CI) or back-transformed estimated means with 95% CI for log-transformed variables (ie, HPCI, IBP, UES IRP, UES Max Ad, UES PP). A, Hypopharyngeal contractility and UES basal pressure; B, Hypopharyngeal intrabolus pressure and UES relaxation and opening metrics; C, UES and proximal esophageal contractile metrics; D, Flow timing metrics and UES relaxation time. \* Displays significant difference versus 10 ml; • indicates versus 20 ml; x indicates versus IDDSI 4. All pairwise comparisons are Bonferroni adjusted. BPT = bolus presence time; DCL = distension-contraction latency; HPCI = hypopharyngeal contractile integral; IBP = hypopharyngeal intrabolus pressure; IDDSI = International Dysphagia Diet Standardization Initiative; PCIes = proximal esophageal contractile integral; UES = upper esophageal sphincter; UES BP = UES basal pressure; UES Max Ad = UES maximum admittance; UES PP = UES peak pressure; UES RT = UES relaxation time; UESCI = UES contractile integral.

## UES and Proximal Esophageal Contractile Metrics

None of the UES contractile parameters (UES BP, UESCI, and UES PP) demonstrated a significant volume effect (Fig. 2A,C). Viscosity only affected UES BP which reduced with a mean difference of 13.2 mmHg (95% CI, 0.8–25.7 mmHg).

Contractility of the proximal esophagus, as measured by PCIes, showed a small effect of volume (mean difference of 5 vs. 10 ml, 77.4 mm Hg·cm·sec [95% CI, 9.7–145.1 mmHg·cm·sec]) and no effect of viscosity, see Figure 2C.

## Flow Timing Metrics and SRI

DCL and BPT showed a significant main effect (P < .001) of bolus type and was affected by both volume and viscosity (Fig. 2D). Volume increased both flow timing metrics across all volume combinations, whereas viscosity reduced DCL and BPT.

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The SRI increased with larger volumes for 5 versus 10 ml and 5 versus 20 ml, but showed no effect of increased viscosity (back-transformed estimated mean of 5 ml thin liquid, 1.3 [95% CI, 1.0–1.8]; 10 ml thin liquid, 2.1 [95% CI, 1.5–2.8]; 20 ml thin liquid, 2.7 [95% CI, 2.0–3.7]; 10 ml thick liquid, 1.6 [95% CI, 1.2–2.1]), see Table II for pairwise comparisons.

## **Time Effects**

Figure 3 shows the mean values of UES BP and UESCI per bolus type per time point. These were the only metrics demonstrating differences in relation to time. Both UES BP and UESCI significantly decreased during the second measurement (time point 2) with an estimated mean difference of 12.0 mmHg (95% CI, 1.0–23.1 mmHg) and 83.8 mmHg cm sec (95% CI, 0.6–167.1 mmHg cm sec), respectively. The estimated mean values of UES BP and UESCI for time point 1 and time point 2 were: 90.0 mmHg

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TABLE II. Main Effect of Bolus Type and Pairwise Comparisons for Bolus Volume and Viscosity.						
Metric (acronym)	Main Bolus Effect	5 vs. 10 ml IDDSI 0	10 vs. 20 ml IDDSI 0	5 vs. 20 ml IDDSI 0	10 ml IDDSI 0 vs. 10 ml IDDSI 4	
Hypopharyngeal contractile integral† (HPCI)	P = .055	0.12 (-0.02 to 0.25)	0.03 (-0.10 to 0.17)	0.15 (-0.03 to 0.32)	-0.06 (-0.23 to 0.12)	
Intrabolus pressure† (IBP)	<i>P</i> < .001	0.30 (0.13 to 0.47)	0.14 (-0.03 to 0.31)	0.44 (0.22 to 0.66)	-0.07 (-0.28 to 0.15)	
Upper esophageal sphincter integrated relaxation pressure† (UES IRP)	P < .001	0.38 (0.19 to 0.56)	0.18 (-0.00 to 0.36)	0.56 (0.33 to 0.78)	0.15 (-0.08 to 0.38)	
UES relaxation time (UES RT)	<b>P</b> < .001	0.03 (0.01 to 0.05)	0.04 (0.02 to 0.06)	0.07 (0.05 to 0.10)	-0.09 (-0.12 to -0.07)	
UES maximum admittance† (UES Max Ad)	P < .001	0.32 (0.26 to 0.39)	0.22 (0.15 to 0.29)	0.54 (0.47 to 0.62)	0.17 (0.09 to 0.24)	
UES basal pressure (UES BP)	<i>P</i> = .001	5.56 (-4.52 to 15.63)	2.93 (-7.25 to 13.10)	8.48 (-3.98 to 20.94)	-13.22 (-25.67 to -0.76)	
UES contractile integral (UESCI)	P = .156	57.76 (-10.60 to 126.13)	-5.85 (-74.82 to 63.12)	51.91 (-34.95 to 138.78)	-26.26 (-113.11 to 60.60)	
UES peak pressure† (UES PP)	P = .179	0.03 (-0.03 to 0.09)	0.02 (-0.04 to 0.08)	0.05 (-0.03 to 0.13)	-0.02 (-0.09 to 0.06)	
Proximal esophageal contractile integral (PCles)	<b>P</b> = .001	77.39 (9.72 to 145.07)	-24.71 (-92.40 to 42.98)	52.68 (-35.80 to 141.16)	36.24 (-52.25 to 124.72)	
Pharyngeal distension- contraction latency (DCL)	<i>P</i> < .001	0.09 (0.06 to 0.12)	0.07 (0.04 to 0.10)	0.16 (0.12 to 0.20)	–0.10 (–0.14 to –0.06)	
Bolus presence time (BPT)	<i>P</i> < .001	0.04 (0.01 to 0.07)	0.05 (0.02 to 0.08)	0.09 (0.05 to 0.13)	-0.11 (-0.15 to -0.07)	
Swallow Risk Index <sup>+</sup> (SRI)	P < .001	0.45 (0.15 to 0.74)	0.28 (-0.02 to 0.58)	0.72 (0.36 to 1.09)	-0.26 (-0.62 to 0.11)	

Estimated mean differences of bolus type 1 (A) vs. bolus type 2 (B); mean difference calculated as B-A. Confidence intervals (95% CI) are shown in parentheses (lower bound to upper bound).

<sup>†</sup>A log-transformed variable with log differences accordingly. Bold text indicates a significant difference.

(95% CI, 79.9–100.2 mmHg) and 78.0 mmHg (95% CI, 67.9–88.1 mmHg); 683.4 mmHg·cm·sec (95% CI, 598.9–768.0 mmHg·cm·sec) and 599.6 mmHg·cm·sec (95% CI, 515.0–684.2 mmHg·cm·sec), respectively.

## DISCUSSION

The present study demonstrates the modulatory response of the pharyngo-esophageal swallow to volume and viscosity using HRPM with impedance. Our use of circumferential pressure sensing technology and randomized test bolus order, in the absence of topical anesthesia, accounted for several limitations of past research of this kind. To our knowledge, this work was also the first to directly examine time effects on physiological swallowing measures. The main findings of this study were: 1) larger bolus volumes increased intrabolus distension pressure, all UES relaxation and opening metrics, pharvngeal flow timing metrics, and the SRI; 2) bolus viscosity increased UES opening and decreased UES relaxation time, preswallow UES basal pressure and pharyngeal flow timing metrics; and 3) pre-swallow UES basal pressure and postswallow UES contractile integral decreased over time.

Several past studies that measured swallowing modulation physiology have used unidirectional pressure sensor technology. Most of the changes to volume reported here confirm previous results found with unidirectional sensing and a fixed order of bolus administration.<sup>26,29,31,32,34</sup> The suggestion that circumferential sensing may be superior, is based on multiple studies that have shown that pressures generated within the pharynx and UES are higher in the anterior-posterior plain.<sup>38-40</sup> However, it is important to recognize that the device we used (Manoscan) calculates a circumferentially averaged value of pressure which is not necessarily equivalent to simultaneous multi-directional measurements achievable only via a "3D-manometry device".<sup>39</sup> Furthermore, parameters that define luminal distension pressure and event timing are less likely to be influenced by the sensor technology used, as these parameters do not rely on quantification of lumen occlusive pressures.<sup>40</sup>

Consistent with most previous reports, higher volumes increased intrabolus distension pressure, UES integrated relaxation pressure, UES relaxation time, UES opening extent, BPT, DCL, and the SRI.<sup>29,31,32,34</sup> No effects were found for UES contractility and UES peak pressure, and only small effects for hypopharyngeal (although not significant) and proximal esophageal contractility were seen, whereas the equivalent results of previous studies were mixed.<sup>31,32,34</sup> As expected from studies that used unidirectional sensing, viscosity increased UES opening extent, decreased UES relaxation time, DCL and BPT, and did not affect hypopharyngeal contractility, UES contractility and UES peak pres-sure.<sup>32,34</sup> Contrary to previous studies,<sup>23,26,32,34</sup> viscosity did not increase intrabolus distension pressure, UES integrated relaxation pressure, proximal esophagus contractility and SRI. However, other investigations of UES relaxation pressure using circumferential pressure sensing also did not find an effect of viscosity on the extent of UES relaxation.<sup>15,27,30</sup>

The present study demonstrated an increase in *pre-swallow* UES basal pressure when thin liquids are swallowed. UES basal pressure was approximately 13 mmHg (17.8%) higher with 10 ml thin liquid swallows when compared to 10 ml thick. However, time also



Fig. 3. A,B, The effect of time on A, Pre-swallow UES basal pressure; B, Post-swallow UES contractile integral; displayed as estimated mean values with 95% confidence interval. T1 = time point 1; T2 = time point 2; UES = upper esophageal sphincter.

affected UES basal pressure resulting in an average decrease of approximately 12 mmHg at the second time point. The thick viscosity bolus was administered last within the swallow protocol, thus the viscosity effect. within each time point, may have also been influenced by time. Nevertheless, our study confirms some<sup>30,34</sup> but not all<sup>15,27</sup> previous reports on pre-swallow UES basal pressure. Ferris and colleagues<sup>34</sup> hypothesized that UES activation occurring early in the swallow sequence may suggest a reflexive pattern to thin fluids which may arrive comparatively earlier at the level of the pharynx and larynx when compared to thick boluses.<sup>41,42</sup> As the differential of pre-swallow activity of the UES between thin and thick viscosity is readily measurable, it may potentially serve as a marker for sensory function. Indeed, quantification of the differential effect of bolus viscosity may provide a better measure, given the influence of time on the UES BP.

## **Clinical Implications**

Most previously reported effects of the swallow modulatory response to volume and viscosity measured with unidirectional sensors were replicated in this study using circumferential pressure sensor technology and a randomized order of bolus administration limiting time and order effects. This confirms that swallow modulation is readily measurable using HRPM with impedance, irrespective of the system, catheter sensor technology and catheter diameter, a relevant factor not tested here.<sup>31</sup> As it is clear that the many modulatory effects reported across different studies are influenced by technology, protocol, and sample size factors, it is important to look at the evidence base as a whole, rather than focusing on any one particular study.

## CONCLUSION

HRPM with or without impedance is being utilized increasingly for the purposes of research and diagnoses. Our study adds to a growing body of literature regarding swallow modulation in healthy subjects. Most of the volume and viscosity effects on standardized swallow meafound to support previous reports. sures were Additionally, longitudinal studies may have to account for time effects as in this study both pre-swallow UES basal pressure and post-swallow UES contractility decreased over time. As the population in this study was young and healthy, further studies are needed to confirm, quantify, and explain these volume, viscosity, and longitudinal effects in older age groups and patient cohorts with different dysphagia-causing etiologies. The results presented in this and in previous articles provide an understanding of normal swallowing physiology as measured by HRPM with impedance. This offers a benchmark for recognizing aberrant pharyngo-esophageal motor responses that may, in turn, inform our understanding of the pathophysiology of swallowing disorders.

#### BIBLIOGRAPHY

- Ertekin C, Aydogdu I. Neurophysiology of swallowing. Clin Neurophysiol 2003;114:2226–2244.
- Cook JJ, Dodds WJ, Dantas RO, et al. Timing of videofluoroscopic, manometric events, and bolus transit during the oral and pharyngeal phases of swallowing. *Dysphagia* 1989;4:8–15.
- Dantas RO, Kern MK, Massey BT, et al. Effect of swallowed bolus variables on oral and pharyngeal phases of swallowing. Am J Physiol 1990;258: G675-G681.
- Lazarus CL, Logemann JA, Rademaker AW, et al. Effects of bolus volume, viscosity, and repeated swallows in nonstroke subjects and stroke patients. Arch Phys Med Rehab 1993;74:1066-1070.
- Jean A. Control of the central swallowing program by inputs from the peripheral receptors - a review. J Autonom Nerv Syst 1984;10:225-233.
- Lang IM. Brain stem control of the phases of swallowing. Dysphagia 2009; 24:333-348.
- Steele CM, Miller AJ. Sensory input pathways and mechanisms in swallowing: a review. Dysphagia 2010;25:323–333.
- Regan J. Impact of sensory stimulation on pharyngo-esophageal swallowing biomechanics in adults with dysphagia: a high-resolution manometry study. *Dysphagia* 2020;35:825–833.
- Jean A. Brain stem control of swallowing: neuronal network and cellular mechanisms. *Physiol Rev* 2001;81:929-969.
- Garcia JM, Chambers E, Molander M. Thickened Liquids. American Journal of Speech-Language Pathology. 2005;14:4–13.
- Logemann JA. Evaluation and Treatment of Swallowing Disorders. second ed. Austin, TX: Pro-Ed; 1998.

- 12. Newman R, Vilardell N, Clave P, Speyer R. Effect of bolus viscosity on the safety and efficacy of swallowing and the kinematics of the swallow response in patients with oropharyngeal dysphagia: white paper by the European Society for Swallowing Disorders (ESSD). Dysphagia 2016;31: 232 - 249
- 13. Tomsen N, Ortega O, Rofes L, et al. Acute and subacute effects of oropharyngeal sensory stimulation with TRPV1 agonists in older patients with oropharyngeal dysphagia: a biomechanical and neurophysiological randomized pilot study. 1756284819842043. Therap AdvGastroenterol 2019:12:
- 14. Ekberg O, Olsson R, Sundgren-Borgstrom P. Relation of bolus size and pharyngeal swallow. Dysphagia 1988;3:69-72.
- 15. Park D, Shin CM, Ryu JS. Effect of different viscosities on pharyngeal pressure during swallowing: a study using high-resolution manometry. Arch Phys Med Rehabil 2017;98:487-494.
- 16. Lee SI, Yoo JY, Kim M, Ryu JS. Changes of timing variables in swallowing of boluses with different viscosities in patients with dysphagia. Arch Phys Med Rehabil 2013;94:120-126.
- 17. Omari TI, Ciucci M, Gozdzikowska K, et al. High-resolution pharyngeal manometry and impedance: protocols and metrics-recommendations of a high-resolution pharyngeal Manometry International Working Group. Dysphagia 2020;35:281-295.
- 18. Omari TI, Rommel N, Szczesniak MM, et al. Assessment of intraluminal impedance for the detection of pharyngeal bolus flow during swallowing in healthy adults. Am J Physiol Gastrointest Liver Physiol 2006;290: G183-G188
- 19. Omari T, Tack J, Rommel N. Impedance as an adjunct to manometric testing to investigate symptoms of dysphagia; what it has failed to do and what it may tell us in the future. United Eur Gastroent 2014;2:355-366.
- 20. Ghosh SK, Pandolfino JE, Zhang Q, Jarosz A, Kahrilas PJ. Deglutitive upper esophageal sphincter relaxation: a study of 75 volunteer subjects using solid-state high-resolution manometry. Am J Physiol Gastrointest Liver Physiol 2006;291:G525-G531.
- 21. Butler SG, Stuart A, Castell D, Russell GB, Koch K, Kemp S. Effects of age, gender, bolus condition, viscosity, and volume on pharyngeal and upper esophageal sphincter pressure and temporal measurements during swallowing. J Speech Lang Hear Res 2009;52:240-253.
- 22. Hoffman MR, Ciucci MR, Mielens JD, Jiang JJ, McCulloch TM. Pharyngeal swallow adaptations to bolus volume measured with high-resolution manometry. Laryngoscope 2010;120:2367–2373.
- 23. Omari T, Kritas S, Cock C. New insights into pharyngo-esophageal bolus transport revealed by pressure-impedance measurement. Neurogastroent Motil 2012;24:e549–e556. 24. Omari TI, Dejaeger E, Tack J, Van Beckevoort D, Rommel N. Effect of bolus
- volume and viscosity on pharyngeal automated impedance manometry variables derived for broad dysphagia patients. Dysphagia 2013;28: 146 - 152
- 25. Lin T, Xu G, Dou Z, Lan Y, Yu F, Jiang L. Effect of bolus volume on pharyngeal swallowing assessed by high-resolution manometry. Physiol Behav 2014.128.46-51
- 26. Omari TI, Kritas S, Cock C, et al. Swallowing dysfunction in healthy older people using pharyngeal pressure-flow analysis. *Neurogastroenterol Motil* 2014;26:59-68.

- 27. Ryu JS, Park D, Oh Y, Lee ST, Kang JY. The effects of bolus volume and texture on pharyngeal pressure events using high-resolution manometry and its comparison with videofluoroscopic swallowing study. J Neurogastroenterol Motil 2016;22:231–239.
- 28. Balasubramanian G, Sharma T, Kern M, Mei L, Sanvanson P, Shaker R. Characterization of pharyngeal peristaltic pressure variability during volitional swallowing in healthy individuals. *Neurogastroenterol Motil* 2017:29:e13119.
- 29. Cock C, Jones CA, Hammer MJ, Omari TI, McCulloch TM. Modulation of upper esophageal sphincter (UES) relaxation and opening during volume swallowing. *Dysphagia* 2017;32:216–224.
  30. Lan Y, Xu GQ, Yu F, Lin T, Jiang LS, Liu F. The effect of bolus consistency.
- on swallowing function measured by high-resolution manometry in healthy volunteers. Laryngoscope 2017;127:173-178.
- 31. Ferris L, Schar M, McCall L, et al. Characterization of swallow modulation in response to bolus volume in healthy subjects accounting for catheter diameter. Laryngoscope 2018;128:1328-1334.
- 32. Schar M, Woods C, Ooi EH, et al. Pathophysiology of swallowing following oropharyngeal surgery for obstructive sleep apnea Neurogastroenterol Motil 2018:30:e13277. syndrome.
- 33. Sia I, Crary MA, Kairalla J, Carnaby GD, Sheplak M, McCulloch T. Bolus volume and viscosity effects on pharyngeal swallowing power-how physiological bolus accommodation affects bolus dynamics. Neurogastroenterol Motil 2018;30:e13481.
- 34. Ferris L, Doeltgen S, Cock C, et al. Modulation of pharyngeal swallowing by bolus volume and viscosity. American Journal of Physiology-Gastrointestinal and Liver Physiology. 2021;320:G43-G53. http://doi.org/10.1152/ajpgi. 00270 2020
- 35. Cajander P, Omari TI, Cock C, Magnuson A, Scheinin M, Savilampi J. Effects of remifentanil on pharyngeal swallowing and esophageal motility - no impact of different bolus volumes, and partial antagonism by methylnaltrexone. Am J Physiol Gastrointest Liver Physiol 2021;321:G367–G377.
- 36. Cichero JA, Lam P, Steele CM, et al. Development of international terminology and definitions for texture-modified foods and thickened fluids used in dysphagia management: the IDDSI framework. Dysphagia 2017;  $32 \cdot 293 - 314$
- 37. Singendonk M, Cock C, Bieckmann L, et al. Reliability of an online analysis platform for pharyngeal high-resolution impedance manometry recordings. Speech, Language and Hearing. 2019;22:195-203.
- 38. Winans CS. The pharyngoesophageal closure mechanism: a manometric study. Gastroenterology 1972;63:768-777.
- 39. Rosen SP, Jones CA, McCulloch TM. Pharyngeal swallowing pressures in the base-of-tongue and hypopharynx regions identified with three-dimensional manometry. *Laryngoscope* 2017;127:1989–1995.
  40. Meyer JP, Jones CA, Walczak CC, McCulloch TM. Three-dimensional manometry of the upper esophageal sphincter in swallowing and non-
- swallowing tasks. Laryngoscope 2016;126:2539-2545.
- 41. Inamoto Y, Saitoh E, Okada S, et al. The effect of bolus viscosity on laryngeal closure in swallowing: kinematic analysis using 320-row area detector CT. Dysphagia 2013;28:33-42.
- 42. Steele CM, Peladeau-Pigeon M, Barbon CAE, et al. Reference values for healthy swallowing across the range from thin to extremely thick liquids. J Speech Lang Hear Res 2019;62:1338-1363.