Modulation of Pharyngeal Swallowing by Bolus Volume and Viscosity

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Conflict of Interest:

Author T Omari holds inventorship of the patent family that covers the analytical methods described. The Swallow Gateway web application is owned by Flinders University. All other authors report no conflict of interest.

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Abstract

Background: Oro-pharyngeal swallowing involves complex neuromodulation to accommodate changing bolus characteristics. The pressure events during deglutitive pharyngeal reconfiguration and bolus flow can be assessed quantitatively using high-resolution pharyngeal manometry (HRPM) with impedance.

Methods: An 8 French solid-state unidirectional catheter (32 pressure sensors, 16 impedance segments) was used to acquire triplicate swallows of 3- to 20- mls across three viscosity levels using a Standardized Bolus Medium (SBMkit) product (Trisco Pty Ltd, Australia). An online platform www.swallowgateway.com (Flinders University, South Australia) was used to semi-automate swallow analysis.

Results: Fifty healthy adults (29 female, 21 male; mean age 46 years; age range 19-78yrs old) were studied. Hypopharyngeal intrabolus pressure, upper esophageal sphincter (UES) maximum admittance, UES relaxation pressure and UES relaxation time revealed the most significant modulation effects to bolus volume and viscosity. Pharyngeal contractility and UES post swallow pressures elevated as bolus volumes increased. Bolus viscosity augmented UES preopening pressure only.

Conclusion: Describing swallow modulatory effects with quantitative methods in line with a core outcome set of metrics, and a unified analysis system for broad reference contributes to diagnostic frameworks for oropharyngeal dysphagia.

New and Noteworthy: The neuromodulation of the healthy oropharyngeal swallow response was described in relation to bolus volume and viscosity challenges, using intraluminal pressure and impedance topography methods. Among a wide range of physiological measures, those indicative of distension pressure, luminal opening and flow timing were most significantly altered by bolus condition, and therefore considered potential markers of swallow neuromodulation. The study methods and associated findings inform a diagnostic framework for swallow assessment in patients with oropharyngeal dysphagia.

Introduction

The oro-pharyngeal swallow response requires complex neuro-regulation (10, 13, 19, 29, 32, 41, 46, 58). During volitional swallowing, bolus characteristics such as volume, taste, viscosity and temperature are detected and relayed to the sensory cortex, and brainstem (19). These sensory inputs enable adaptation of the swallow system for optimal bolus transfer from the oral cavity to the esophagus.

The pressure events associated with the swallowing motor response can be recorded using high-resolution pharyngeal manometry (HRPM) (15, 17, 22, 30, 33, 49, 51, 52, 56) and bolus flow events can be assessed when HRPM is integrated with impedance measurement (4, 5, 9, 14, 25, 26, 37, 42, 54-56). Using this combined technique with automated analysis methods, a rich, objective dataset of pressure and flow measurements can be acquired and used to detect the swallow motor response in relation to bolus characteristics (6, 26, 31, 36, 56, 57). Most recently, a core outcome set of parameters and protocols for HRPM with impedance assessment has been suggested (39), providing a standardized approach to recording and reporting HRPM measurements.

Bolus texture modification and volume regulation are regularly implemented in dysphagia management with the intention to slow bolus flow, enhance bolus control, and optimize swallow initiation and airway protection (28, 50), however, until now, the respondent swallow mechanics have not been comprehensively documented (35, 60). Additionally, in clinical practice, optimal viscosity levels for oropharyngeal dysphagia (OPD) treatment in the individual patient need to be ascertained more discriminately across dysphagia-causing etiologies (2). Age-related changes to swallow physiology are well recognized, particularly in adults over 60 years of age (7). Gender has less impact on pharyngeal and UES contractility (3, 33, 56), with only small

effects seen for longer pharyngeal pressure duration in females (3), and there is greater pharyngeal pressure during cued effortful swallowing (33).

The effects of bolus volume (8, 13, 14, 17, 21, 33, 53), and viscosity (23, 33, 53, 56), on unimpaired swallowing biomechanics have previously been documented with high-resolution manometry. This study characterized the oro-pharyngeal swallow response to a wider than previously studied, range of bolus volumes and consistencies using HRPM with impedance. We aimed to determine which, of a recently established suite of core outcome metrics (39) and set of novel bio-mechanical measures were most influenced by bolus condition, accounting for age and gender effects. We tested the following hypothesis: parameters indicative of distension and flow-timing would be the most responsive and therefore could, in the future, function as diagnostic markers to detect impaired swallow modulation in patients with dysphagia.

Method

Study cohort

This prospective study was approved by the Southern Adelaide Clinical Human Research Ethics Committee (SAC HREC EC00188). Healthy adults were enrolled between the ages of 18 – 80 years unless they met the following exclusion criteria: previous abdominal or head & neck surgery; subject reported swallowing difficulties or symptoms of heartburn or regurgitation; uncontrolled diabetes; blood pressure abnormalities; pregnancy; allergy to local anesthesia; and medication affecting gastrointestinal motility. Any daily medications were assessed by the study doctor (author CC) before enrolment. Dysphagia screening was conducted and produced normal scores from the DAKKAK score (12) and Sydney Swallowing Questionnaire (62). All manometry investigations were performed in the Gastroenterology & Hepatology Department at Flinders Medical Centre. In compliance with ethical requirements each participant was provided

100 with refreshments on completion of the protocol, observed for 30 minutes and then contacted 24
101 hours following participation.

102 **High-resolution pharyngeal manometry with impedance**

103 An 8 French solid-state unidirectional high-resolution manometry catheter (32 pressure sensors
104 at 1cm, 16, 2 cm length impedance segments, Unisensor/Laborie, Attikon, Switzerland) was
105 used for data collection. Inbuilt catheter sensors detected pressures along the swallowing tract
106 from velopharynx to proximal esophagus. Adjacent impedance electrode segments
107 simultaneously detected bolus contact. Following data acquisition, each de-identified pressure-
108 impedance file was exported as an ASCII file and uploaded to the Swallow Gateway™ web-
109 application for analysis (57).

110 **Test bolus formulation and swallow protocol**

111 Participants were fasted for a minimum of three hours, and prior to catheter positioning
112 Lidocaine spray (5%) was applied to one nostril. Participants were tested while seated in a head
113 neutral, upright position. The HRPm protocol for each participant involved triplicate cued
114 swallow challenges across 12 liquid bolus conditions (total 36 swallows) administered via
115 syringe. The conditions comprised three consistencies (thin, mildly thick and extremely thick;
116 see below) and four volumes (3, 5, 10 and 20ml). Prior to any bolus administration, participants
117 were informed to attempt single swallows per bolus through the study, however, were assured
118 that multiple swallows were not to be avoided if felt to be required. The fluid consistencies for
119 the protocol were prepared using the Standardized Bolus Medium (SBMkit) product (Trisco Pty
120 Ltd, Australia), purpose-formulated to optimize stable bolus electrical conductivity properties
121 across all bolus consistencies, ensuring reliability of impedance-based measurements. The
122 SBMkit comprises an apple flavored, sodium chloride (NaCl) concentrate solution, and a

separate gum-based thickener (Precise Thick'N Instant), which during preparation are added to tap water. The International Dysphagia Diet Standardization Initiative (IDDSI) protocols (59) were used to confirm mildly thick (IDDSI level 2 by 10 second syringe drip test) and extremely thick (IDDSI level 4 by spoon tilt test), and a HAAKE Viscotester 550TM viscometer (Thermo Electron, Karlsruhe, Germany) was used to assess the shear viscosity values of 137.37 ± 5.16 mPa·s (IDDSI 2) and 637.49 ± 33.71 mPa·s (IDDSI 4) at 50s^{-1} (batch number 59676), by using 10.27g and 30.83 gr in ionic solution till 200ml.

Swallow Gateway analysis

Data were exported to the Swallow Gateway™ online application for analysis (www.swallowgateway.com; owned and provided by Flinders University, Adelaide, South Australia). Swallow analysis was conducted by author LF and cross-checked by author TO. While blinded analysis would be optimal, bias is minimized by the semi-automated swallow analysis methods. Results were generated in accordance with a recommended core outcome set (39), and novel (additional to core outcome set) Swallow Gateway™-specific metrics were also derived; see Table 1 for a complete list of parameters and definitions. For the most part, the recommended core outcome set describes four key types of bio-mechanical phenomena: lumen occlusive pressures at the velopharynx, mesopharynx, hypopharynx, and UES; hypopharyngeal intrabolus pressures (IBP); UES opening extent, and UES relaxation. Analytic methods and reliability of Swallow Gateway™ analysis have previously been described (57). Pharyngeal swallows are selected from the manometric tracing and labelled according to bolus administration. In this study, piecemeal swallows were excluded from analysis as a reduction in bolus volume seen with piecemeal swallows is known to alter swallow biomechanics. Figure 1A demonstrates the selection of spatial and temporal landmarks, which define the boundaries for semi-automated analysis. Swallow parameters that have previously been correlated with

pathophysiological outcomes, e.g. radiologically confirmed aspiration (6, 41, 55), are then derived.

Statistical analysis

The average results for each of the 12 swallow test conditions were tabulated in an Excel spreadsheet for statistical analysis using SPSS (IBM Corp. IBM Statistical Package for the Social Sciences [SPSS] Statistics for Windows, v. 25.0 Armonk, NY: IBM Corp). Data with a skewed distribution were normalized by log transformation prior to analysis. The main effects of volume, viscosity, age and gender were evaluated using generalized linear mixed model. Bonferroni adjustment was applied to pairwise comparisons.

Results

Fifty healthy volunteers (mean age 46yrs; age range 19-78yrs old; 29 females, 21 males) were included in this study and group characteristics are outlined in Table 2. Participants were grouped <60yrs or >60yrs as age related changes in healthy swallowing have been shown to commence around 60 years of age (11, 14, 20, 33, 53). The manometry procedure was well-tolerated across the cohort. One participant had difficulties with the catheter in situ, therefore a limited number of swallows were acquired for this subject. Piecemeal swallowing, whereby the orally administered bolus is swallowed in portions, rather than in whole, was observed for 38 swallows (6%) across 27 individuals. Results from piecemeal swallows were removed to ensure the data in this study represent single swallow bolus transfer per volume given. However, normal reference ranges of un-cued piecemeal swallowing across larger bolus volumes in future studies would have clinical utility. All results for main effects are presented in Table 3.

Core outcome set variables

Pharyngeal Lumen occlusive pressures: Pharyngeal, Velopharyngeal, Mesopharyngeal, and Hypopharyngeal Contractile Integrals

Lumen occlusive pressures measured as contractile integrals (CI) of the pharynx were augmented as bolus volume increased. Pairwise comparisons are displayed in Figure 2A. A significant main effect of volume was observed for contractility at the level of velopharynx (VCI) ($F=9.27$, $p<0.001$), and hypopharynx (HPCI) ($F=2.87$, $p=0.04$) (Table 3). Pairwise differences between volumes were observed for VCI (Figure 2A). Viscosity did not affect pharyngeal contractility (see Table 3 and Figure 2A). Age did not affect overall pharyngeal contractility as defined by PhCI, however, older subjects demonstrated evidence of reduced velo- and mesopharyngeal contractility ($F=7.29$, $p<0.007$, and $F=8.98$, $p=0.003$ respectively; Table 3). A large gender effect was seen, with male participants showing greater contractility of the pharynx overall ($F=95.24$, $p<0.001$), as well as greater velo- and mesopharyngeal contractility compared to female participants ($F=54.87$, $p<0.001$ and $F=181.2$, $p<0.001$ respectively).

Hypopharyngeal intrabolus pressure

Hypopharyngeal intrabolus pressures (IBP) were altered by both increased volumes and viscosity (main effects $F=26.30$, $p<0.001$, and $F=10.49$, $p<0.001$ respectively). Significant pairwise differences were observed across all volume combinations with greater IBP observed with larger volumes ($p<0.005$) and viscosity combinations (IDDSI level 0 vs. level 2 $p=0.03$, vs. level 4 $p<0.001$, and level 2 vs. level 4 $p<0.05$) (Figure 2D). Older subjects showed a trend towards higher IBP values ($F=3.36$, $p=0.07$), while male subjects demonstrated overall lower IBP values compared to females ($F=12.06$ $p=0.001$).

UES relaxation pressure

Like IBP, UES integrated relaxation pressures (UES IRP) demonstrated significant main effects seen with increased UES IRP observed for increased volume and viscosity ($F=43.47$, $p<0.001$ and $F=35.93$, $p<0.001$, respectively). Significant pairwise differences are depicted in Figure 2D. UES IRP increased with age ($F=21.71$, $p<0.001$), and, in contrast to the IBP, was higher in male vs female subjects ($F=9.03$, $p=0.003$).

UES relaxation duration and opening extent: UES max. admittance, UES relaxation time

UES relaxation time increased with higher bolus volume swallows (main effect $F=32.87$, $p<0.001$; see Figure 2 for pairwise comparisons) but was reduced during heavier viscosity swallows ($F=9.25$, $p<0.001$). UES opening, as measured using UES maximum admittance (UES max ad), revealed the most sensitive findings across this study based on the size of main effect and number of pairwise differences. Both volume and viscosity increase the UES max ad ($F=383.2$, $p<0.001$ and $F=51.84$, $p<0.001$ respectively; pairwise comparisons are shown in Figure 2D).

Additional swallow function variables

UES Contractile Pressures: UES basal pressure, UESCI, UES peak pressure and Proximal Esophageal Contractile Integral

A small numerical increase in pre-swallow UES basal pressure was seen with larger bolus volumes (Figure 2C), however this did not reach significance. In contrast, bolus viscosity had a significant main effect in reducing UES basal pressure ($F=10.08$, $p<0.001$), with pairwise significance for 10ml volumes only IDDSI level 0 vs. level 2; $p=0.05$, level 4, $p=0.02$ (Figure 2C). A significant increase in post-swallow activity of the UES was observed with larger bolus sizes as demonstrated based on a higher UES contractile integral (UESCI) (main effect $F=4.78$,

p=0.003), and UES peak pressure (main effect $F=3.98$, $p=0.008$). Pairwise differences between volumes were observed for UESCI nor UES peak pressure (see Figure 2B). Viscosity affected neither UESCI, nor UES peak pressure.

Age had no effect on UES basal pressure or UESCI, but a significant increase in UES peak pressure was seen for participants >60yrs ($F=38.13$, $p<0.001$). Male subjects demonstrated a significantly higher UES basal pressure, UES peak pressure and UESCI compared to female participants ($F=69.40$, $p<0.001$, $F=50.14$, $p<0.001$, and $F=83.73$, $p<0.001$ respectively).

The activity of the proximal esophagus was highly responsive to bolus conditions, with proximal esophageal contractile integral (PCI) increasing with both volume (main effect $F=20.13$, $p<0.001$) and viscosity (main effect $F=7.88$, $p<0.001$) (Figure 2B). Age had no effect on PCI, however male subjects had significantly increased PCI measurements compared to female participants ($F=20.22$, $p<0.001$).

Pharyngeal Flow Timing and Bolus Presence: DCL and BPT

There were significant main effects of volume and viscosity on timing variables. Distension to contraction latency (DCL) and bolus presence time (BPT) were lengthened by volume ($F=71.93$, $p<0.001$ and $F=31.61$, $p<0.001$ respectively) and were shortened by viscosity ($F=14.09$, $p<0.001$ and $F=8.59$, $p<0.001$) (Figure 2E). Age had no effect on DCL and BPT, but a significant gender effect ($F=5.35$, $p=0.02$ and $F=14.00$, $p<0.001$) was observed with male participants showing increased DCL compared to females.

Swallow Risk Index: SRI

Swallow Risk Index (SRI), a global composite score designed to capitalize on the directionality of aberrant swallow parameters, increased as bolus volume and viscosity increased (main

effects $F=31.71$, $p<0.001$ and $F=3.19$, $p=0.04$ respectively). The SRI increased in older age groups ($F=4.55$, $p=0.03$) and was reduced in males ($F=3.98$, $p=0.05$).

Discussion

In this study, we utilized a unidirectional sensor state-of-the-art manometry-impedance technique to characterize the oro-pharyngeal swallow response in relation to a wide range of bolus conditions using an extensive series of established swallow function parameters. The main findings were: i) the healthy swallow response was overall more finely tuned and modified in relation to bolus volume than bolus viscosity, with larger boluses leading to greater pressure generation, ii) the parameters quantifying bolus distension area, distension pressure and distension timing were more sensitive than contractile measures, for detecting bolus-related modulation of the swallow system, iii) viscosity changes were found to alter UES pre-swallow basal pressure, bolus flow timing and UES relaxation duration, and iv) age and gender effects were also seen, most notably, a decrease in pharyngeal contractility with age and reduced UES relaxation in older and male participants. Altogether these findings define the biomechanical features associated with the oro-pharyngeal swallow response in health, providing a benchmark for assessment of these features in patients with OPD.

Pharyngeal, UES and proximal esophageal contractility measures

With increasing bolus volumes, we observed modulatory responses to pharyngeal contractility. The largest increases were seen in the velo-pharyngeal contractile integral (VCI), reflecting pressures that seal the pharyngeal chamber proximally, which is in line with previous research (14, 33, 53). The observed change in contractility indicates greater force generation as a larger bolus volume is propelled. UES post swallow pressures also increased with increasing bolus

volumes; and it has been suggested that this contraction helps to prevent retrograde bolus return immediately post swallow (47). Of interest, increased bolus viscosity had little or no effect on the VCI or any other pharyngeal contractility measurements. This is in line with some previous work (33, 53), while others have reported reduced pharyngeal contractility, measured as maximum pressure values, with increased viscosity (23). In relation to the hypopharynx specifically, the current study detected a small overall increase in hypopharyngeal contractility with increasing volume, and increased hypopharyngeal IBP was also observed. This is in line with previous research (13), and is discussed below. We believe a larger sample size in this current study may have revealed the subtle pharyngeal contractility changes we note.

Overall, our findings have demonstrated a more pronounced stimulus from bolus volume, compared to bolus viscosity for modulation of the pharyngeal swallowing motor program. However, interestingly, the pre-relaxation UES basal pressure was significantly augmented for thinner bolus consistencies, an effect that was most pronounced at 10ml volumes, and while this is not widely documented it corresponds with another recent report (23). This may suggest an anticipatory activation of the UES during the earliest phases of the swallow motor response i.e. in concert with earlier onset of hyolaryngeal excursion and earlier CP muscle relaxation that occur to accommodate thinner fluids, which arrive earlier at the airway opening (8). Furthermore, an element of UES volitional control has recently been shown, whereby healthy volunteers were trained with manometric biofeedback to elevate or reduce UES pressure (34). This suggests that pre-swallow UES basal pressure may be influenced by preparatory central and possible volitional factors. In general, the UES pre-swallow contraction is thought to assist in the creation of negative pressures within the proximal esophagus which, upon UES opening, causes a bolus suction effect that facilitates bolus transfer into the esophagus (18, 29, 43). This suction effect is associated with negative nadir UES relaxation pressures, a biomechanical feature which was apparent in our participants, particularly during smaller volume swallows.

Observations in relation to proximal peristalsis of the esophageal body are not widely reported in the literature when compared to the pharynx and distal esophagus. However, in the current study, we observed marked effects of bolus condition on proximal esophageal contractility. Indeed, the proximal esophageal contractile integral (PCI) was by far the most responsive of all reported contractile measures, increasing significantly with both liquid volume size and viscosity level. Experimental luminal fluid distention of the esophagus in isolation is well known to initiate secondary peristalsis as well as a range of other specific esophageal and UES contractile reflexes governed by central and enteric nervous system circuits (4, 14, 24, 53, 56). Activation of some mechanoreceptor-initiated peripheral circuits is also likely to occur during volitional bolus swallowing. Their effects are potentially superimposed leading to alteration of the esophageal contractile response. Our data show that the fluid bolus conditions that generated the highest lumen distension pressures during bolus transport were associated with the greatest level of proximal esophageal contractile response. Importantly, the broad-based responsiveness of the proximal esophagus to physiological bolus distensions differed to the pharyngeal regions which only showed volume-related increases in contractility, despite viscosity level also being a potent driver for distension pressure, as is described below.

Pharyngeal and UES distension measures

Using a variety of acquisition methods, measurements and swallow protocols, previous research has established that larger bolus volumes are associated with higher pharyngeal distension pressures and longer UES opening to accommodate earlier arrival of the bolus (4, 14, 53, 56). Results from this study highlight three metrics (each relating to the proficiency of UES relaxation and opening), which responded significantly to increases in volume and viscosity. These were: i. hypopharyngeal intrabolus pressure (IBP), ii. UES maximum admittance, and iii. UES integrated relaxation pressure (IRP). Age and gender effects in this study also confirm their sensitivity for detecting subtle changes within an otherwise normally

functioning system (33, 38). Our results suggest these metrics are key markers of swallow modulation.

Elevated hypopharyngeal intrabolus pressure is known to flag possible UES outflow obstruction in patients as upstream hypopharyngeal pressures elevate with increased viscosity, increased trans-sphincteric bolus flow rate, reduced UES aperture, and/or reduced hypopharyngeal and/or UES distensibility (18, 46, 63). The observed effects of age and gender possibly indicate a subtle reduction in compensatory reserve in older individuals, and possibly larger pharyngeal chambers overall in males able to accommodate the bolus challenges with less impact on IBP compared to female participants. Understanding normal IBP modulation may assist in assessment and interpretation of difficult dysphagia cases with and without obvious features of UES dysfunction.

UES maximum admittance, a marker of UES opening extent (5), detected differences at all volume increments across all viscosity levels. This was the only metric able to distinguish between 3 and 5ml volumes for both thin and mildly thickened fluids. Maximum admittance has previously been described as a non-specific marker of reduced UES opening (5), with low admittance values flagging impaired bolus driving forces and/or UES luminal restriction. Additionally, the UES pressures during relaxation and reception of the propelled bolus (UES IRP) were progressively elevated as the volume and viscosity increased, as has previously been shown with high resolution manometry (33). With significant pairwise comparisons between lower and higher volumes and consistencies, and differences for age and gender, the sensitive alterations of UES opening and relaxation pressures demonstrate the potential for these measures to be used to detect not only overt but also subtle swallow modulation dysfunction.

Flow timing measures

The current study shows that distension, relaxation and contractility timing are key physiological features of the pharyngeal swallow response that are substantially altered in relation to bolus conditions. This is perhaps not surprising as the optimal timing and coordination of bolus arrival with luminal opening and closure serves to minimize resistance to bolus flow and optimize airway protection in a healthy swallow system (10, 13). The components of UES opening, achieved by hyolaryngeal excursion, bolus propulsive forces and CP muscle deactivation are all thought to be influenced by bolus volume, and modified via central pattern modulation in the brainstem (4). In this study, UES relaxation time increased with larger bolus volume as has been shown in previous work (27), whereas increasing bolus viscosity decreased UES relaxation time in our study. It is likely that faster moving boluses, as seen with larger volumes and thinner bolus types, are associated with an earlier onset of UES relaxation when compared to a heavier and slower bolus (18); this has previously been shown in smaller volumes (23). In contrast to our current findings, a recent radiological study of a <60yr old cohort reported no effect of viscosity on UES opening duration. However, they showed swallow reaction time was significantly later with thicker bolus types (60), and time to laryngeal vestibule closure was shorter, both relative to a later hyoid elevation movement and a prompter airway protective response once the hyoid movement commenced (60).

Pharyngeal distension is influenced by lingual propulsion, which facilitates timely arrival of a cohesive bolus ahead of the pharyngeal stripping wave. Timing between pharyngeal distension and contractility (DCL), and overall bolus presence time in the pharynx (BPT), revealed similar results to UES relaxation time. Longer durations of DCL and BPT were seen in response to larger volumes, however durations were shorter in response to increased viscosity. This can be explained by the relatively later arrival of a thicker bolus into the pharyngeal chamber compared to a thin fluid, which flows faster and therefore arrives comparatively 'earlier' in the swallow sequence in relation to the pharyngeal contraction, which is largely stereotypical in its timing.

Overall, this study demonstrates flow-timing metrics which are sensitive to volume changes and discriminated all increments for each separate viscosity level. All timing metrics are therefore potentially useful clinical markers of aberrant swallow modulation and potentially useful markers of swallow improvement when fluid viscosity is modified.

Swallow Risk Index

Finally, the SRI increased with volume, viscosity, age, and gender. The SRI has previously proven useful in dysphagia assessment and has been proposed as a global marker of swallow dysfunction (5-7, 54, 55). Our study supports this concept, showing that the SRI has sufficient sensitivity to detect bolus condition changes. The SRI increase, albeit within normal limits, seen with increased viscosity is driven by a correlated increase in IBP and a reduced DCL measure with more viscous boluses. These two individual metrics are responding as we would expect to increased viscosity however, their contribution within the SRI formula amplifies the index comparative to thin fluid swallows. In patients with evidence of pre-swallow pharyngeal bolus presence, the SRI decreases with viscosity (40). Together with the subtle alterations related to age and gender effects, our findings suggest an abnormal SRI may be a useful global measure to detect inadequate swallow modulation.

Limitations

This study is limited in that measurements undertaken using HRPM with impedance were not directly correlated with videofluoroscopy, as radiation exposure was unjustified. We note that several previous manometry studies have reported and validated the physiological measures against radiological outcomes in both healthy controls and patients with dysphagia, albeit with varying acquisition methods and protocols (29, 32, 41, 46). Unidirectional pressure sensors along the catheter assembly may have produced variability within pressure readings, therefore

confirmation of these study findings with circumferential pressure sensor techniques will be valuable in future studies. Bolus volumes and viscosity challenges in our study were undertaken in a fixed order, rather than randomized protocol. Therefore, data may be subject to time and order effects. With this extensive protocol, which spanned up to 30 minutes, sensory accommodation may have influenced the results. Our findings must be interpreted in relation to known viscosity-based rheological constructs. We have provided standardized measurements with gum based thickening agent bolus preparations tailored to the IDDSI recommendations, which can vary greatly within each broad IDDSI-based viscosity level, particularly between gum vs. starch based thickening agents (16, 45, 60). However, in this study the gum-based bolus media underwent rheological testing at the IDDSI specified viscosities. We have included these data for completeness and translatability. Future HRPM with impedance studies could explore differences between gum and starch based thickening agents, and precise bolus rheological characteristics such as elasticity, adhesiveness, cohesiveness (2) and shear thinning qualities (44, 48), which may influence swallow biomechanics.

Strengths of the study were a sample size permitting adequately powered statistical analysis, and balance for age and gender effects. This study adds to the current literature a comprehensive report of healthy swallow modulation relating to a range of bolus volume and viscosity conditions not previously reported. A set of normative values can now be referenced within clinical practice. The use of www.swallowgateway.com software, now generalized for routine use to derive consensus-recommended, as well as novel analytics, enables further investigations across centers and study cohorts to both confirm and extend our findings. Beyond the effects of texture modification and volume regulation, neuro-stimulants are increasingly under investigation for their use as OPD treatments (1, 61) and future studies could explore the biomechanical implications with HRPM and impedance methods.

Conclusion

Describing swallow modulatory effects comprehensively in healthy participants, with a core outcome set and a unified analysis system, represents a further step towards optimizing diagnostic frameworks for oropharyngeal dysphagia. We report key swallowing modulation measures in response to a thorough set of volume and viscosity ranges using standardized and experimental HRPM and impedance parameters. Some findings of this study were confirmatory of established knowledge, however other subtle and key differences not previously documented are highlighted and present as important biomechanical indicators of healthy swallow modulation. From the recommended core outcome set (39) hypopharyngeal intrabolus pressure, UES maximum admittance, UES relaxation pressure and UES relaxation time, altered most significantly with bolus condition. Further exploration in dysphagia patients will substantiate these results and determine the clinical value of these measures which have previously been difficult to achieve.

Figures and Tables

Figure 1. Panel A: Example of a pressure topography swallow plot. Panel B: Integrated pharyngeal pressure profile and impedance/admittance curves. Panel C: Integrated UES pressure profile and impedance/admittance curves. Abbreviated pressure flow measures incorporated in the figure to correspond with definitions in Table 1.

Figure 2. Graphs showing effects of volume and viscosity for A: pharyngeal contractility measures; B: UES contractility measures, and proximal esophageal contractility; C: UES Basal pressure; D: pharyngeal and UES distension measures; and E: Pressure flow Timing measures. * depicts Bonferroni adjusted pairwise significance vs. 20ml volumes; # vs. 10mls and ^ vs. 5mls. □ depicts Bonferroni adjusted pairwise significance vs. IDDSI level 0; Ⓢ vs. IDDSI level 2.

Table 1. Core Outcome Set Metrics and Additional to Core Outcome Set Metrics, with pressure-flow subtype, measurement label with abbreviation, and definitions.

Table 2. Participant characteristics from Group 1 & 2. Mean (range) results for swallow screening using the DAKKAK and SSQ questionnaires are presented. Mean (SD) for Core Outcome Set and Additional to Core Outcome Set Metrics presented. # indicates statistical significance ($p < 0.05$) vs. Group 1.

Table 3. Summary of Main Effects from General Linear Mixed Modelling (GLMM) with F statistic and P values presented. ↑ indicates directionality of effect with increasing volume/viscosity/age/male gender. * measures were log transformed prior to GLMM. Bold results indicate metrics which showed statistical significance following Bonferroni adjustments.

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D Pharyngeal and UES distension measures

E Pressure flow timing measures

CORE OUTCOME SET METRICS		
Measurement Subtype	Measurement	Definitions (28)
<i>Pharyngeal lumen occlusive pressures</i>	Pharyngeal contractile integral (PhCI)	An integral pressure measure of pharyngeal contractile vigor spanning from the velopharynx to the upper margin of the UES (mmHg.cm.s).
	Velopharyngeal contractile integral (VCI)	An integral pressure measure of pharyngeal contractile vigor spanning the velopharyngeal region only (mmHg.cm.s).
	Mesopharyngeal contractile integral (MCI)	An integral pressure measure of pharyngeal contractile vigor spanning the mesopharyngeal region only (mmHg.cm.s).
	Hypopharyngeal contractile integral (HPCI)	An integral pressure measure of pharyngeal contractile vigor spanning the hypopharyngeal region only (mmHg.cm.s).
<i>Hypopharyngeal intrabolus distension pressure</i>	Hypopharyngeal intrabolus distension pressure (IBP)	The pressure 1 cm superior to the UES apogee position at the time of maximum hypopharyngeal distension (indicated by impedance/admittance) (mmHg).
<i>UES relaxation & opening</i>	UES integrated relaxation pressure (UES IRP)	A pressure measure of the extent of UES relaxation pressure, generated as the median of the lowest pressure in a non-consecutive 0.20–0.25 second window (mmHg).
	UES relaxation time (UES RT)	A measure of the duration of UES relaxation – a pressure interval below 50% of baseline or 35 mmHg, whichever is lower, in units of seconds (s).
	UES maximum admittance (UES Max Ad)	A measure of extent of UES opening. The highest admittance value (inverse of impedance) recorded during trans-sphincteric bolus flow, in units of millisiemens (mS).

ADDITIONAL TO CORE OUTCOME SET SWALLOW GATEWAY™ SPECIFIC METRICS		
Variable Subtype	Variable	Definition
UES contractile measure	Upper esophageal sphincter contractile integral (UESCI)	An integral pressure measure of UES contractile vigor, post swallow (mmHg.cm.s).
	UES basal pressure (UES BP)	The peak pressure at the level of the UES pre swallow (mmHg).
	UES peak pressure (UES PP)	The peak pressure at the level of the UES measured immediately post pharyngeal contraction (mmHg).
Proximal esophageal contractile measure	Proximal esophageal contractile integral (PCI)	An integral pressure measure of proximal esophageal contractility (mmHg.cm.s).
Flow Timing Variables	Pharyngeal Distension-Contraction Latency (DCL)	A timing measure from maximum pharyngeal distension to the pharyngeal luminal occlusive contraction – a correlate of how well the bolus is propelled ahead of the pharyngeal stripping wave, (in milliseconds).
	Bolus Presence Time (BPT)	The dwell time of the bolus in the pharynx (in milliseconds).
Global Swallow Risk Index	Swallow Risk Index (SRI)	A composite formula score designed to capitalize on the directionality of aberrant swallow parameters. The original report described SRI in patients with neuro-muscular disease and aspiration on radiology (14).

	Group 1 (18-59yrs)	Group 2 (60-80yrs)
N	36	14
Mean age (yrs)	37 (19-57)	68 (61-78)
Gender	13 F, 6 M	8 F, 9 M
Mean DAKKAK score	0.19 (0-3.5)	0 (0-0)
Mean SSQ score	45 (0-169)	24 (0-67)
Core Outcome Set Swallow Metrics (definitions in Table 1) Grand Means (SD)		
PhCI (mmHg.cm.s)	253 (96)	237 (105)
VCI (mmHg.cm.s)	80 (49)	70 (46) [#]
MCI (mmHg.cm.s)	107 (45)	103 (64)
HPCI (mmHg.cm.s)	66 (33)	64 (29)
IBP (mmHg)	2.8 (6.2)	3.4 (6.3)
UES IRP (mmHg)	-3.6 (4.8)	-1.8 (5.1) [#]
UES RT (s)	0.53 (0.09)	0.52 (0.10)
UES Max Ad (mS)	5.25 (1.22)	5.06 (1.14)
Additional Swallow Gateway™ Specific Metrics (definitions in Table 1) Grand Means (SD)		
UESCI (mmHg.cm.s)	428 (200)	436 (208)
UES BP (mmHg)	64 (32)	68 (45)
UES PP (mmHg)	251 (5)	312 (8) [#]
PCI (mmHg.cm.s)	285 (9)	286 (12)
DCL (s)	0.47 (0.09)	0.46 (0.09)
BPT (s)	0.62 (0.16)	0.61 (0.17)
SRI	1.71 (2.08)	1.74 (1.71)

CORE OUTCOME SET METRICS						
Variable Subtype	Variable	GLMM parameters	Volume Effect	Viscosity Effect	Age Effect	Gender Effect
Pharyngeal lumen occlusive pressure	Pharyngeal contractile integral (PhCI)	<i>F</i> <i>P</i>	↑ 5.42 0.001	0.74 ns	2.01 ns	↑ 95.24 <0.001
	Velopharyngeal contractile integral (VCI) *	<i>F</i> <i>P</i>	↑ 9.27 <0.001	0.07 ns	↓ 7.29 0.007	↑ 54.87 <0.001
	Mesopharyngeal contractile integral (MCI) *	<i>F</i> <i>P</i>	0.46 ns	0.23 ns	↓ 8.98 0.003	↑ 181.2 <0.001
	Hypopharyngeal contractile integral (HPCI)	<i>F</i> <i>P</i>	↑ 2.87 0.04	1.53 ns	0.67 ns	1.29 ns
Hypopharyngeal intrabolus distension pressure	Hypopharyngeal intrabolus distension pressure (IBP)	<i>F</i> <i>P</i>	↑ 26.30 <0.001	↑ 10.49 <0.001	↑3.36 0.07	↓ 12.06 0.001
UES relaxation & opening	UES integrated relaxation pressure (UES IRP)	<i>F</i> <i>P</i>	↑ 43.47 <0.001	↑ 35.93 <0.001	↑ 21.71 <0.001	↑ 9.03 0.003
	UES relaxation time (UES RT) *	<i>F</i> <i>P</i>	↑ 32.87 <0.001	↓ 9.25 <0.001	1.21 ns	↑ 43.49 <0.001
	UES maximum admittance (UES Max Ad)	<i>F</i> <i>P</i>	↑ 383.2 <0.001	↑ 51.84 <0.001	↓ 7.68 0.006	↓ 19.62 <0.001

ADDITIONAL TO CORE OUTCOME SET SWALLOW GATEWAY™ SPECIFIC METRICS						
Variable Subtype	Variable	GLMM parameters	Volume Effect	Viscosity Effect	Age Effect	Gender Effect
UES contractile measures	Upper esophageal sphincter contractile integral (UESCI) *	<i>F</i> <i>P</i>	↑ 4.78 0.003	1.81 ns	1.05 ns	↑ 83.73 <0.001
	UES basal pressure (UES BP) *	<i>F</i> <i>P</i>	0.33 ns	↓ 10.08 <0.001	0.32 ns	↑ 69.40 <0.001
	UES peak pressure (UES PP)	<i>F</i> <i>P</i>	↑ 3.98 0.008	1.46 ns	↑ 38.13 <0.001	↑ 50.14 <0.001
Proximal esophageal contractile measure	Proximal esophageal contractile Integral (PCI)	<i>F</i> <i>P</i>	↑ 20.13 <0.001	↑ 7.88 <0.001	0.005 ns	↑ 20.22 <0.001
Flow Timing measures	Pharyngeal Distension-Contraction Latency (DCL)	<i>F</i> <i>P</i>	↑ 71.93 <0.001	↓ 14.09 <0.001	2.22 ns	↑ 5.35 0.02
	Bolus Presence Time (BPT) *	<i>F</i> <i>P</i>	↑ 31.61 <0.001	↓ 8.59 <0.001	0.34 ns	↑ 14.00 0.001
Global Swallow Risk Index	Swallow Risk Index (SRI) *	<i>F</i> <i>P</i>	↑ 31.71 <0.001	↑ 3.19 0.04	↑ 4.55 0.03	↓ 3.98 0.05

High Resolution Pharyngeal Manometry Pressure Topography

Adjust heatmap threshold

Pressure & Impedance/Admittance Data Graphs