Temporal Sequence of ~~Upper Esophageal Sphincter Opening and~~ Laryngeal Vestibule Closure and Reopening is Associated with Airway Protection

Short Title: Temporal sequence affects airway protection

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Acknowledgements: The research reported in this publication was supported by the Eunice Kennedy Shriver National Institute of Child Health & Human Development of the National Institutes of Health under Award Number R01HD092239, and the data was collected under Award Number R01HD074819. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Conflicts of Interests: The authors have no conflicts of interest to declare.

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Abstract

Background: Upper esophageal sphincter opening (UESO), and laryngeal vestibule closure (LVC) are two essential kinematic events whose timings are crucial for adequate bolus clearance and airway protection during swallowing. ~~The~~Their temporal characteristics ~~of these events~~ can be quantified ~~in~~ through time-consuming analysis of videofluoroscopic swallow studies. **Objectives:** We sought to establish a model to predict the ~~presence~~odds of penetration or aspiration during swallowing based on 15 temporal factors of ~~UESO~~UES and ~~LVC in videofluoroscopic images.~~laryngeal vestibule kinematics. **Methods:** Manual measurements for the ~~onset and offset of~~ UESO~~ and~~, UES closure, LVC ~~kinematic events~~, laryngeal reopening (LVO), and ratings of ~~laryngeal~~ penetration and aspiration were conducted on a videofluoroscopic dataset of 408 swallows from 99 patients. A generalized estimating equation model was deployed to analyze association between individual temporal factors and the risk of penetration or aspiration. **Results:** The results indicated that the latencies of laryngeal vestibular events and the time lapse between UESO onset and LVC were highly related to penetration or aspiration. The predictive model incorporating patient demographics and bolus presentation showed that delayed LVC by 0.1s or delayed ~~laryngeal reopening~~LVO by 1% of the swallow duration (average 0.018s) was associated with a 17.19% and 2.68% increase in odds of airway invasion, respectively. These results demonstrate that a delay of one-half second in LVC or LVO would increase the odds of laryngeal penetration or aspiration during oral intake by 86% or 74%. **Conclusion:** This predictive model provides insight into kinematic factors that underscore the interaction between the ~~timing of UESO and airway protection. Further refinement of our methods is warranted to improve the objectivity of the clinical diagnosis. Likewise, the treatment of dysphagia may be positively influenced by considering temporal kinematic patterns of UESO and LVC with sophisticated algorithms~~intricate timing of laryngeal kinematics and airway protection. Recent investigation in automatic non-invasive or videofluoroscopic detection of laryngeal kinematics would provide clinician access to objective measurements not commonly quantified in VFSS studies. Consequently, the temporal and sequential understanding of these kinematics may interpret such measurements to an estimation of the risk of aspiration or penetration which would give rise to rapid computer-assisted dysphagia diagnosis.

Keywords: Aspiration, Dysphagia, Videofluoroscopic swallow studies, Upper esophageal sphincter, Laryngeal vestibule closure.

Level of Evidence: 2

Introduction

Dysphagia is a swallowing disorder that affects up to 30-40% of older individuals and is highly prevalent among populations with head/neck cancer, neurological diseases, and iatrogenic conditions.[1-3] Patients with dysphagia are at risk of aspirating material into the lungs, which may result in aspiration pneumonia and other complications such as malnutrition and dehydration[1]; therefore, comprehensive evaluation of aspiration risk using all available information is critical in initiating and managing dysphagia treatment.

Videofluoroscopic swallow studies (VFSS) allow real-time observation of swallowing physiology and offer precise assessment of swallowing kinematics.[4] From VFSS images, clinicians and researchers can use the standardized 8-point penetration-aspiration scale (PAS) to evaluate the presence and depth of swallowed material in the airway.[5] Additionally, they can perform temporal ~~analysis~~and spatial analyses of swallowing kinematics to determine significant deviations from the norms for sequential swallowing events.[6,7,8] Unfortunately, ~~temporal analysis is time-consuming and many clinicians do not use this objective measurement~~only 16% of speech-language pathologists responding to ~~informa~~a research survey indicated that they perform frame-by-frame measurements on their ~~clinical impressions.~~VFSS studies more than 80% of the time, with a full 32% indicating that they never perform measurements.[48] VFSS studies are structured to sample swallow physiology of typical foods and liquids in a person's diet and are meant to characterize swallowing that occurs throughout the day; however, people swallow hundreds of times per day and only a limited number of swallows (*e.g., 10-20) can be observed on VFSS due to radiation safety concerns.

During swallowing, a variety of biomechanical events occur over the very short duration of about 1 second, including upper esophageal sphincter opening (UESO) and laryngeal vestibule closure (LVC). Both events are directly related to other kinematics~~(e.g.,~~: hyolaryngeal excursion contributes to the sealing of the larynx and pulls open the UES[46]; intrabolus pressure ~~generation).~~is generated in balance with reduced UES muscle tension and anterior traction of cricoid cartilage[47]. At rest, the airway is continuously open. The pattern of swallowing momentarily shifts the pharynx from the respiratory mode to the deglutitive mode, closing the larynx and opening the UES, in a sequential manner that enables bolus transport into the esophagus while breathing is interrupted. Therefore, the fine temporal coordination and sufficient duration of UESO and LVC are crucial for safe and effective swallowing.[9]

The sequential relation between airway closure and UESO have been studied in healthy populations. Kendall et al[10] observed that the onset of aryepiglottic fold elevation always occurs before UESO and complete supraglottic closure occurs almost always prior to the UESO among healthy volunteers~~.~~ for liquid swallows regardless of volume. While Molfenter et al[11] confirmed that the onset of airway closure commonly occurs before UESO, they disagreed with certain obligatory ordering proposed by Kendall et al. and further concluded that the overall swallowing sequence is highly variable across young healthy adults and repeated trials. Herzberg et al[12] found the less common sequence of UESO and laryngeal closure (LVC after UESO) happened predominantly among older participants but less frequently among younger ones. ~~More recently, reference values of temporal UESO and LVC measurements were extracted from healthy young adults by Steele et al[13]. Their findings indicated that UESO occurred just before LVC (average time lapse 0.046 s) and UES closure occurred simultaneously or before the laryngeal reopening (average time lapse 0.03 s) in most cases.~~All 3 above-mentioned studies reported no clear influence of bolus viscosity on swallowing sequences but suggested that smaller bolus volume might exceptionally cause greater sequence variations. To summarize, current investigations fail to establish a universal obligatory sequence between LVC and UESO for healthy swallows; variable sequencing between these events have been noticed across different bolus volumes, bolus consistencies, participants' ages, and even repeated trials.

Other studies considered UESO and LVC latencies (the start of the event referenced to the beginning of the swallow or other events), durations, and the time intervals between these events as swallowing characteristics.[11] Steele et al[13] extracted reference values of temporal UESO and LVC measurements from healthy young adults. Their findings indicated that the average time lapse between UESO and LVC is 0.046 s and UES closure occurred about 0.03 s before the laryngeal reopening in average. Park et al[14] observed significantly delayed initiation and reduced duration of laryngeal closure among patients with stroke who aspirated~~.~~ versus who did not aspirate. Nativ-Zeltzer ~~and Logemann[15]~~et al.[15] found significantly longer ~~UESO and~~ LVC latencies in relation to differences in glossopalatal junction (the oropharyngeal portal) opening for the participants who aspirate and penetrated compared to the healthy ones but longer UESO to glossopalatal junction opening only for patients who aspirated versus normal participants. Kiyohara et al[16] identified the prolonged time interval between the start of laryngeal elevation to LVC favoring penetration or aspiration during hyolaryngeal displacement, as well as the premature opening of the LVC during its descent. Both videofluoroscopic and manometric studies revealed the association of post-stroke aspiration with shorter UESO duration.[17,18] In addition, Saconato et al[19] reported longer duration of supraglottic closure for poststroke patients who aspirated than the patients who did not; however, the duration of UESO was not found significant regardless of volume and consistency. ~~Furthermore~~Besides variables measuring individual UESO or LVC, Choi et al[20] and Curtis et al[21] considered ~~time lapse~~temporal relations between laryngeal events and UESO among patients with dysphagia and patients with Parkinson's diseases but neither discovered ~~its~~their association to aspiration. Although various temporal measures of UESO and LVC have been examined in the literature, there is no consistent conclusion on which latencies or sequential relations between these events are the most influential and to what extent they influence swallowing safety.

Our overarching aim in this line of research is to automate and objectify some aspects of human judgment of VFSS study observations, particularly events that are not commonly measured objectively, into the domain of objective data that clinicians can use in analyzing swallowing function. Consequently, the present study sought to estimate the risk of penetration or aspiration in patients suspected of having dysphagia based on the temporal variables (i.e., initiation, termination, duration, and relative time lapse of UESO and LVC) extracted from videofluoroscopic image sequence analyses. ~~The~~This is the first research we are aware of in which the duration of pharyngeal swallow segments was used as a temporal factor to normalize the variables~~.~~ across different swallows. Our hypothesis is that these raw or normalized temporal variables of UESO and LVC are associated with aspiration or penetration. We aimed to determine the most significant correlates ~~and assess~~of airway protection impairments and quantify how the risk of airway invasion changes as a function of these attributes ~~via a~~(e.g., how do odds of aspiration change for each increment of temporal event latency?) via a novel repeated-measure multivariable model, into which we further integrated patient demographics and bolus conditions.

Materials and Methods

Data Collection

The protocol of this study was approved by the Institutional Review Board of the University of Pittsburgh. All participants provided written informed consent. Patients with suspected dysphagia referred for a VFSS at the University of Pittsburgh Medical Center Presbyterian University Hospital (Pittsburgh, PA) were recruited. Each patient underwent VFSS conducted by a speech language pathologist who determined the bolus size, bolus consistency, and swallowing maneuver according to patients' conditions under standard clinical protocol. Only swallows with thin liquid boluses (Varibar thin, Bracco Diagnostics, Inc., < 5 cPs viscosity) were considered in the present analysis. Boluses were either self-administered by patients via a cup or a straw for uncued swallows or administered by a clinician using a spoon for cued swallows.

During the VFSS examination, patients were positioned laterally to a standard x-ray machine (Ultimax system, Toshiba, Tustin, CA) at 30 pulses per second with their head in a neutral position. The video stream was captured by AccuStream Express HD (Foresight Imaging, Chelmsford, MA) at a sampling frequency of 30 frames per second.

VFSS Image Analysis

The dataset of this study was accrued during an ongoing larger investigation of surface pharyngeal electronic sensors in characterizing swallow physiology.[22] Data from the sensors were not a component of the present study. All video clips were preliminarily segmented into individual swallowing events. The swallow onset (or initiation of the pharyngeal phase) was defined as when the head of bolus reached the posterior ramus of the mandible, and the swallow offset was defined as when the hyoid bone returned to the lowest position and the bolus has cleared from pharynx. This duration has historically been defined as pharyngeal transit duration.[23] The UES region is considered approximately the height of the third cervical vertebral body inferiorly from the top edge of tracheal column.[24] The timing measurements of UESO and LVC were marked for each swallow according to the following criteria:

- **UESO onset**: The time of the first frame in which air or barium contrast is observed in the UES region.[25]
- **UESO offset**: The time of the first frame in which air or barium contrast is completely cleared from the UES region.[24]
- **LVC**: The time of the first frame in which air space is no longer visible in the laryngeal vestibule (between the arytenoids and epiglottic base).[26]
- **Laryngeal vestibule reopening (LVO)**: The time of the first frame of obvious air space reappearance within the laryngeal vestibule.[26]

All temporal and clinical measurements (i.e., PAS) were performed by trained judges who were blinded to patients' demographics and diagnoses. Reliability of judges was established a priori and was maintained on an ongoing basis with excellent intra- and inter-rater reliability (> 0.99 intraclass correlation coefficients) on a randomly selected 10% of the swallows to avoid judgment drifts.

A set of temporal variables were calculated using the previously described timing measurements to explore the timing of UESO and LVC events. Previous studies employed the onset of the swallow as an anchor to calculate the onset of UESO[27] and the initiation of LVC[14,20,21] (or bolus dwell time[28]). Similarly, we computed the latencies between the swallow onset and each component event (closing/opening of UES and laryngeal vestibule). Additional variables were calculated to describe their durations and temporal relations. These variables were either represented in seconds, or by the ratio of the time interval to the swallow duration, which normalized the timing events to the individuals' swallows:

1. Swallow/pharyngeal transit duration (s): The time difference between swallow onset and swallow offset.
2. UESO-latency (s): The time difference between swallow onset and UESO onset.
3. UESC-latency (s): The time difference between swallow onset and UESO offset.
4. LVC-latency (s): The time difference between swallow onset and LVC.
5. LVO-latency (s): The time difference between swallow onset and LVO.
6. UESO-normalized-ratio (% swallow duration): The ratio between UESO-latency and swallow duration.
7. UESC-normalized-ratio (% swallow duration): The ratio between UESC-latency and swallow duration.
8. LVC-normalized-ratio (% swallow duration): The ratio between LVC-latency and swallow duration.
9. LVO-normalized-ratio (% swallow duration): The ratio between LVO-latency and swallow duration.
10. UESO-duration (s): The time difference between UESO latency and UESC latency.

11. LVC-duration (s): The time difference between LVC latency and LVO latency.
12. UESO-duration-normalized-ratio (% swallow duration): The ratio between UESO-duration and swallow duration.
13. LVC-duration-normalized-ratio (% swallow duration): The ratio between LVC-duration and swallow duration.
14. UESO-LVC-duration-normalized-ratio (% swallow duration): The time difference between UESO-latency and LVC-latency divided by swallow duration.
15. LVO-UESC-duration-normalized-ratio (% swallow duration): The time difference between LVO-latency and UESC-latency divided by swallow duration.

Statistical Analysis

The presence of penetration or aspiration was a dichotomous variable based on PAS ratings. PAS scores of 1-2 represented safe swallows, while PAS ≥ 3 corresponded to penetration or aspiration (unsafe swallows).[7] We collected more than one swallow for each participant so correlations may exist between repeated swallow measurements from the same patients[29]; consequently, a generalized estimating equation (GEE) model with a binomial distribution, logit link function, and exchangeable working correlation matrix was used to associate each of the 15 temporal variables with penetration or aspiration. To obtain a parsimonious multivariable model, we used a forward selection strategy of the 15 temporal variables with and without forcing in the demographics and bolus characteristics as independent variables. Previous literature has reported an age effect on sequential swallow events, citing significant differences in event sequencing and latencies between healthy younger (<45 years) and older (>65 years) subjects.[12,30] However, most of our patients were older than 60 years and the correlation between temporal variables and age was negligible; thus, age was treated as a continuous variable. All statistical analyses were performed using SAS® version 9.4 (SAS Institute, Inc., Cary, North Carolina).

Results

We analyzed 408 swallows from 99 patients whose demographics and bolus characteristics are presented in Table 1. Swallows grouped by PAS scores are shown in Table 2. ~~A~~The most common sequential pattern of UESO and LVC, which represented 76% of our study, is shown in Figure 1 (it should be noted that UESO onset can occur before or after LVC, and UES closure can happen before or after laryngeal reopening[26]).

The averaged values of temporal variables and the results of one-at-a-time statistical analysis with and without demographics and bolus conditions adjustment are shown in Table 3. In both unadjusted and adjusted models, swallows with unsafe airway protection (i.e., PAS $\geq$ 3) had significantly later occurrences of LVC, LVO, LVC-normalized-ratio, and LVO-normalized-ratio as compared to safe swallows (i.e., PAS 1-2). In addition, a longer time lapse in the UESO-LVC-duration-normalized-ratio contributed to an increased risk of airway invasion. The latency of UESO, duration of LVC, and the LVO-UESC-duration-normalized-ratio were not significantly associated with penetration or aspiration.

The parsimonious multivariable model identified included only laryngeal kinematics: LVC-latency and LVO-normalized-ratio as shown in Table 4. Delayed LVO in proportion to the swallow duration and delayed LVC latency resulted in increased airway invasion risk.

Table 5 presents the associations when using the combination of temporal variables with patients' ages, sex, and mode of bolus administration (e.g., 3mL by spoon; patient self-selected volume by cup, straw). The forward selection on the adjusted set of variables resulted in the same set of kinematic variables (i.e., LVO-ratio and LVC-frame) as the unadjusted model with consistent estimates of coefficients. According to the adjusted model, delayed LVC by 0.1s results in a 17.19% increase in the odds of airway invasion. Delayed LVO by 1% of the swallow duration (average 0.018s) would cause the participant to have 2.68% more odds to penetrate or aspirate. In consequence, 1s delay on LVC latency or late LVO ratio by 55.7% of the swallow duration (average 1s) would substantially magnify these odds by 4.9 (odds ratio [OR] 4.89; 95% confidence interval [CI] 1.94–12.29) or 4.4 (OR 4.37; 95% CI 1.96–9.71) times respectively. Results indicated that each 10 years of age will increase patients' odds of penetration or aspiration by 16.07~~%,~~% and females are less likely to experience unsafe swallows, but ~~this effect is~~these effects are not statistically significant. ~~Female and~~However, self-feeding by cup ~~are less likely to experience unsafe swallows~~is significantly associated with lower risk of airway invasion.

Discussion

In this study, we sought to determine whether the kinematic timings associated with laryngeal and UES kinematics are predictive of penetration or aspiration among patients with suspected dysphagia. We specifically examined the singular and coordinated temporal variables of UESO and LVC, for which the sequential characteristics have not been fully established. A temporal normalization based on the duration of swallow segments was applied to align temporal swallowing patterns across different patients~~ to explore new analytics methods of identifying airway protection risk when there are no sentinel events during the VFSS (i.e., moderate impairment, when airway invasion risk is neither absent nor severe, and clinical risk estimations are more subjective).~~.

The LVC latency was found to be different between safe and unsafe swallows, which is consistent with previous work on stroke patients[31]; however, the delayed latency of LVO was also significantly associated with penetration or aspiration, which has rarely been considered as a predictor. This finding may suggest that the timing and pattern of laryngeal reopening, but not necessarily the *duration of LVC*, are critical for airway protection. Counterintuitively, delayed laryngeal reopening did not improve airway protection in our cohort; this may be due changes in the duration and timing of swallow apnea among patients with respiratory illnesses and a subsequently higher risk of aspiration or penetration.[32,33]

According to our analyses, ~~UES-related latencies~~UESO latency and UESO durations were ~~not~~only found associated with penetration or aspiration in adjusted analyses and were not selected in our final prediction models; however, reduced UESO duration and delayed initiation of UESO have shown to be ~~influential~~determinants of aspiration.[20,28] The discrepancy between existing literature and our findings may be the result of variations in the definitions of disordered groups. Previous studies placed patients with at least one abnormal swallow, defined as PAS ≥ ~~3~~3[28] or PAS ≥ ~~6~~6[20], into disordered/aspirated swallow groups. Conversely, we analyzed single swallow events, instead of placing patients into categories, and considered a PAS ≥ 3 an unsafe swallow sample. We chose to analyze single swallow events because a) healthy individuals may have more than one abnormal swallow according to PAS on a VFSS,[34] but we would not place them in a disordered swallow group and b) patients who typically aspirate may not during the short window of time of the VFSS, so it would not be accurate to place them in a "normal swallow" group.[7,30]

We also found that the shorter time lapse between LVC and UESO onset (i.e., UESO-LVC-duration-normalized-ratio) was significantly associated with penetration or aspiration, suggesting that late laryngeal closure prior to UESO and even after UESO may lead to swallowed material entering the airway and may cause incomplete bolus clearance. This finding was not observed previously, because Choi et al[20] defined the region of UES ~~differently~~by the narrowest part of the upper esophagus between C4 and C6 which is different from our study and chose intervals between the UESO and laryngeal elevation instead of laryngeal closure. Furthermore, Curtis et al[21] specifically analyzed patients with Parkinson's disease and dysphagia while our study considered participants with various medical conditions. However, this variable is excluded from the final multivariate models which may be due to its collinearity with LVC latencies which are better predictors of aspiration or penetration.

Although the duration of a swallow segment was not correlated with airway invasion, the smaller ratio of the LVC and LVO latencies to swallow duration were associated with increased risk. In addition, the final models suggested that the LVO normalized latency was a better predictor than the raw measurement of the LVO, indicating that with same latencies of laryngeal vestibule events, swallows with shorter duration are more likely to be unsafe.

~~Our~~Despite of the fact that age was not significantly associated to penetration or aspiration, our final model -suggested that older people probably are at greater risk ~~for penetration or aspiration~~ as demonstrated in previous studies.[35,36] The results also indicated that although the difference between men and women was not significant, females appeared less likely to aspirate or penetrate~~.~~; this finding may be due to the imbalance of gender distribution in our dataset; this finding may be due to the imbalance of gender distribution in our dataset. Boluses administrated by clinicians using spoons were more likely to cause airway invasion than self-administrated boluses by cup, possibly because aspiration is more affected by cueing and administering conditions than bolus volume.[21,37]

We believe our findings are essential to add objectivity and accuracy to swallowing assessment. Objective measurements of laryngeal-pharyngeal kinematics provide information about the functional integrity of structures responsible for airway protection. In neurodegenerative diseases, for instance, serial quantification of subtle kinematic indicators of airway protection risk may not manifest as frank aspiration during VFSS studies but are predictive of eventual clinically significant decompensation in airway protection. However, the reality of clinical work combined with the need for clinicians to manually analyze each swallow using existing time-consuming methods, leads clinicians to forgo objective measurements to inform their clinical impressions out of clinical expediency, and form subjective inferences about predicted risk and outcomes (e.g., aspiration) when they do not overtly occur during a VFSS study. Recent technological advancements enable non-invasive detection of swallowing kinematic events solely based on swallowing sounds and vibrations (i.e., high resolution cervical auscultation).[40-45] Other computer vision and artificial intelligence techniques were applied to VFSS images for automatic frame-by-frame analyses of hyoid[49] and laryngeal[50] kinematics. The laryngeal measurements automatically extracted by these methods could be incorporated to our temporal understanding of laryngeal kinematics associated with swallowing efficiency and safety to provide clinicians objective estimation of the risk of penetration or aspiration. Such automated generation and analysis of objective data followed by clinician confirmation and clinical interpretation, as is commonly performed with electrocardiograms and some imaging studies, would provide baseline and ongoing information about progression of dysphagia, efficacy of treatment, and enable clinicians to objectively predict actual present and future risks associated with oropharyngeal dysphagia rather than forming a subjective judgment that can lead to either over- or under-treatment.

There are several limitations of current study. Our dataset consists of only thin liquid boluses; thus, the developed prediction model does not explain how patients' risk of aspiration would be affected by boluses of different consistencies as delineated in the International Dysphagia Diet Standardization Initiative.

In addition to temporal measurements considered in our study, other physiological factors that contribute to airway protection were missing to provide a full analysis of swallowing safety and efficiency. For example, reduced UESO may cause post-swallow residue, which is an independent predictor of penetration or aspiration post-swallow.[38] Future studies should investigate the association between the timing of UESO with residue-rating methods such as the Modified Barium Study Impairment Profile.[28,39]

Furthermore, the distribution of PAS scores is naturally skewed and swallows with higher aspiration or penetration risk are in minority. This imbalance distribution might affect the classification performance of our models. Data sampling and augmentation techniques may be used for future studies.

~~Recent technological advancements enable non-invasive detection of swallowing kinematic events solely based on swallowing sounds and vibrations (i.e., high resolution cervical auscultation).[40-45] Hence, further understanding of how these temporal measurements reflect swallowing impairment may add valuable diagnostic information to ongoing research in this field.~~

In this study, we normalized kinematic timings using swallow duration. This conversion allowed us to conduct a more general analysis of swallowing motor pattern among various patients and different bolus conditions. The validity of such normalization is an avenue for further investigation.

Conclusion

This study demonstrated that the delayed latency of LVC and delayed LVO proportional to swallow segment duration ~~reflect~~ is associated with the risk of penetration or aspiration ~~risk~~ of thin liquid swallows. The model is based on ~~objective~~ temporal measurements, patient demographics, and bolus delivery methods ~~estimated~~to estimate the ~~patients'~~patient's risk of airway invasion. ~~These findings provide supportive information~~The underlying association of laryngeal kinematics and penetration or aspiration would provide justification to perform objective temporal VFSS analyses when ~~diagnosing~~a) the delay of kinematics is too short to be perceived by human eye, b) no apparent sign of swallowing ~~disorders and further improvement of the model would~~ impairment can be observed during a 10-20 swallows VFSS examination. With recent advancement in non-invasive kinematic detection and computer-assisted VFSS analyses, modest delay of laryngeal kinematics can be captured, and therefore our findings would add more objectivity and accuracy to automated swallowing assessment and dysphagia management.

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Figure Legends

FIGURE 1. Upper esophageal sphincter opening (UESO), and laryngeal vestibule closure (LVC) events occur in sequential manner based on videofluoroscopic analysis.