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Differences in timing between functional swallows of older adults at risk for dysphagia and healthy older and young adults

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Differences in timing between functional swallows of older adults at risk for dysphagia and healthy older and young adults

Original Version

Ph. D. Thesis presented to the Posgraduate Program in Medicine at the Ribeirão Preto Medical School, University of São Paulo to obtain the degree of Doctor in Medicine. Concentration area: Biomedicine Investigation
Advisor: Prof. Dr. Roberto Oliveira Dantas
Co-advisor: Prof. Dr. Catriona Margaret Steele

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I dedicate this work to the many patients and their families. For sharing with me the daily quest for a more comfortable life for our loved ones. The ones who entrust me for their treatments and give me lessons of infinite love and surpassing. You are the reason to be better every day.

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‘The Master said: Is there anything more pleasant
than studyng with perseverance?’

Confucius

LIST OF TABLES

LIST OF FIGURES

LIST OF ABREVIATIONS

AEES	Abertura do Esfíncter Esofágico Superior
ASPEKT	Analysis of Swallowing Physiology: Events, Kinematics & Timing
BPM	Bolus Passing Mandible
C4	Cervical Vertebra Number 4
C6	Cervical Vertebra Number 6
cc	cubic centimeters
CI	Confidence Interval
DSG	Dorsal Swallowing Group
EAT-10	Eating Assessment Tool
EDG	Elderly at Risk of Dysphagia Group
EES	Esfíncter Esofágico Superior
EHG	Healthy Elderly Group
FVL	Fechamento do Vestíbulo Laríngeo
HCRP	Hospital das Clínicas de Ribeirão Preto
LCI	Confidence Interval Lower Bondary
LV	Laryngeal Vestibule
LVC	Laryngeal Vestibule Closure
LVCRT	Laryngeal Vestibule Closure Reaction Time
LVO	Laryngeal Vestibule Opening
MPC	Maximum Pharyngeal Constriction
NTS	Nucleus Tractus Solitarius
ms	milliseconds
NED	National Elderly Policy
OPMR	Oropharyngeal Motor Response
PAS	Penetration-Aspiration Scale
SD	Standard Deviation
SUS	Brazilian Public Health System
TPR	Transient Potencial Ion Channel Receptors
TRI	Toronto Rehabilitation Institute
TRPA1	Transient Potencial Ion Channel Receptors

	Subfamily A Member 1
TRPM8	Transient Potencial Ion Channel Receptors Subfamily M Member 8
TRPV1	Transient Potencial Ion Channel Receptors Subfamily V Member 1
UCI	Confidence Interval Upper Bondary
UES	Upper Esophageal Sphincter
UESO	Upper Esophageal Sphincter Opening
VSG	Ventral Swallowing Group
WHO	World Health Organization
YHG	Healthy Young Adults Group

Abstract

Nascimento, WV. Differences in timing between functional swallows of older adults at risk for dysphagia and healthy older and young adults. 96p. [Thesis] Ribeirão Preto Medical School-USP. Ribeirão Preto -SP, 2018.

Introduction: As with other functions, the aging process can cause changes in swallowing, even in asymptomatic individuals. **Purpose:** 1. To determine whether timing measures for swallows from healthy older adults differ from comparison measures for healthy young adults. 2. To determine whether timing measures for functional swallows from older adults at risk of dysphagia differ from comparison measures for healthy older adults. 3 To determine whether differences in timing explain the occurrence of transient penetration of material into the airway (Penetration-Aspiration Scale scores of 2) in any of these groups. **Method:** Duplicate blinded ratings were obtained for swallows of 20%w/v thin liquid barium collected under videofluoroscopy at 30 frames/s from 17 healthy older adults, aged 60-84 (12 women). Swallows were compared to data from a retrospective dataset collected in 20 healthy young adults aged 22-45 (10 women) and functional swallows (Penetration-Aspiration Scale scores <3) of 11 older adults at risk for dysphagia, aged 62-87 (3 women). Eight timing measures were studied, including parameters related to swallow response, bolus transit, laryngeal vestibule closure and upper esophageal sphincter (UES) function. We used linear mixed model repeated measures ANOVAs to explore the hypothesis that swallow timing measures would be longer in the older adults than in young adults, and even longer in the older adults at risk for dysphagia. **Results:** Consistent with the hypotheses, significantly longer swallow reaction time, UES opening (UESO) duration, the interval from laryngeal vestibule closure (LVC) to UESO ($p<0.01$) and the interval following UESO to maximum pharyngeal constriction (MPC) were seen in the healthy older participants compared to the young healthy controls. Furthermore, a significantly longer interval from the onset of hyoid movement to UES opening, and longer laryngeal vestibule closure reaction time (LVCRT), ($p<0.01$) were seen in the older participants at risk of dysphagia in comparison with healthy older adults. Also, this group presented longer intervals from LVC to UES opening and from maximum pharyngeal constriction to UES closure. For both the healthy young group and the healthy elderly group, in cases where transient penetration of material into the laryngeal vestibule was seen, laryngeal vestibule closure reaction time was longer and laryngeal vestibule closure occurred late, after UES opening. For both the healthy elderly group and elderly at risk of dysphagia, when penetration was observed, a shorter interval from hyoid onset to upper esophageal sphincter opening was seen. Also, laryngeal vestibule closure was late and there was a longer LVC to UESO interval when penetration occurred. Finally, laryngeal vestibule closure duration was shorter in case of penetration in the elderly group at risk of dysphagia **Conclusions:** Longer swallow timing measures, in general, distinguish swallows in healthy older adults from swallows in young healthy adults, and in older adults at risk of dysphagia from healthy older adults. In cases of transient penetration, laryngeal vestibule closure was delayed.

Keywords: 1. Ageing, 2. Timing measures, 3. Swallowing

Resumo

Nascimento, WV. Diferenças nas medidas temporais de deglutiçoes funcionais de idosos em risco de disfagia e idosos e jovens adultos saudáveis. 96f. [Tese] - Faculdade de Medicina de Ribeirão Preto-USP. Ribeirão Preto -SP, 2018.

Introdução: Tal como acontece com outras funções, o processo de envelhecimento pode causar alterações na deglutição, mesmo em indivíduos assintomáticos. **Objetivo:** 1. Determinar se as medidas temporais da deglutição diferem entre idosos saudáveis e adultos jovens saudáveis. 2. Determinar se as medidas temporais de deglutições funcionais de idosos em risco de disfagia diferem das medidas de idosos saudáveis. 3 Determinar se diferenças nas medidas temporais explicam a ocorrência de penetração transitória (escore PAS igual a 2) em qualquer desses grupos. **Método**: Foram realizadas análises cegas duplicadas para deglutições de bário líquido diluído a 20%, coletadas em videofluoroscopia a 30 quadros/s de 17 idosos saudáveis, entre 60 e 84 anos (12 mulheres). As deglutições foram comparadas a um banco de dados coletado retrospectivamente de 20 jovens jovens saudáveis entre 22 e 45 anos (10 mulheres) e deglutições funcionais (escores da Escala Penetração-Aspiração <3) de 11 idosos com risco de disfagia, com idade entre 62-87 (3 mulheres). Foram estudadas oito medidas temporais, incluindo parâmetros relacionados à resposta à deglutição, trânsito do bolo, fechamento do vestíbulo laríngeo e função do esfíncter esofágico superior (EES). Utilizamos análise de medidas repetidas em modelos mistos lineares ANOVAs para explorar a hipótese de que as medidas temporais da deglutição seriam maiores nos idosos do que em adultos jovens e ainda maiores nos idosos em risco de disfagia. **Resultados:** De acordo com as hipóteses, para resposta à deglutição (SRT), duração da abertura do EES (AEES), do intervalo entre o fechamento do vestíbulo laríngeo (FVL) para AEES (p <0,01) e do intervalo entre AEES até a constrição máxima da faringe foram observadas medidas significantemente aumentadas no grupo idosos saudáveis em comparação com jovens saudáveis. Além disso, um intervalo significativamente mais longo desde o início do movimento do hióide até a abertura da EES e longo tempo de reação para o fechamento do vestíbulo laríngeo (p <0,01) foram observados nos participantes idosos em risco de disfagia em comparação com idosos saudáveis. Além disso, este grupo apresentou intervalos mais longos entre FVL e AEES e entre a constrição máxima da faríngea e o fechamento do EES. Tanto para o grupo jovem saudável como para o grupo idoso saudável, nos casos em que a penetração transitória do material no vestíbulo laríngeo foi observada, o tempo de reação para fechamento do vestíbulo laríngeo foi maior e o fechamento do vestíbulo laríngeo ocorreu de forma tardia, após a abertura do EES. Tanto para o grupo de idosos saudáveis quanto para os idosos em risco de disfagia, quando ocorreu penetração, observou-se um intervalo menor entre o início do movimento do hióide e a abertura do esfíncter superior do esôfago. Além disso, o FVL estava atrasado e houve um intervalo prolongado entre FVL e AEES quando ocorreu a penetração. Finalmente, a duração do fechamento do vestíbulo laríngeo foi menor em caso de penetração no grupo idoso em risco de disfagia. **Conclusões:** medidas de tempo de deglutição prolongada, em geral, são um fator claro que distingue as deglutições de idosos saudáveis e deglutições de jovens saudáveis, e de idosos em risco de disfagia e de idosos saudáveis. Quando uma penetração transitória foi encontrada, o mecanismo de fechamento do vestíbulo laríngeo apresentava-se atrasado.

Palavras-chave: 1. Envelhecimento, 2. Medidas temporais, 3. Deglutição

SUMMARY

Introduction

1. INTRODUCTION

1.1 Swallowing function

The capacity to perform safe and efficient swallowing is one of the most basic human needs. It is important for nutrition, hydration and quality of life[1].

The upper aerodigestive tract has two basic functions, breathing and swallowing. The oropharyngeal motor response (OPMR) is composed of coordinated movements of the oropharyngeal structures that reconfigure the respiratory tract to a digestive tract for swallowing, and which return the tract into a pathway for breathing once the bolus has moved into the esophagus [2][3]. These configuration changes are produced by the coordinated opening and closing of the glossopalatal junction, the velopharyngeal junction, the laryngeal vestibule (LV) and the upper esophageal sphincter (UES) [4][5].

Usually, descriptions of swallowing divide the process into three or four phases: the oral phase (which is often further subdivided into an oral preparatory phase and an oral propulsive phase), the pharyngeal phase and the esophageal phase[6][7][8][9]. Each of these phases will be discussed below, with identification both of the events that occur and of the neural sensorimotor control mechanisms that govern these events. At a neurophysiological level, swallowing is a complex function that requires sensorimotor integration and coordination of multiple anatomical structures, muscles, nerves and brain [10][11][12].

1.1.1 Oral Preparatory Phase

The oral preparatory phase is completely voluntary and its main function is the formation of the bolus. Two different processes have been described to take place during oral bolus formation, depending on whether the bolus is a solid food or a liquid[13]. With solid foods, the tongue directs the bolus onto the occlusal surface of the teeth for chewing. The mastication process is characterized by cyclical mandibular movements. The tongue and cheeks work together to maintain the bolus on the molar surface of the teeth. Saliva plays a key role as it hydrates, lubricates and begins the digestion of the food during bolus formation thanks to the enzyme α-amylase [14][15][16]. With liquids, there is no need for chewing. Instead, the bolus is typically held in a chamber on the upper surface of the tongue, and the back of the tongue raises to create contact with the soft palate, forming a seal at the glossopalatal junction that prevents the bolus from falling prematurely into the pharynx.

The oral preparatory phase represents a key opportunity for peripheral receptors to capture sensory information about the bolus and communicate this information to the brain regions involved in swallowing control. This includes information regarding characteristics of the bolus, in terms of taste, aroma, chemical composition, temperature, volume and consistency [(10)(17)(18)(19)(20)(21)]. Taste information is detected by the receptors housed in the taste buds, which are distributed throughout different areas of the oral cavity. Taste receptors in the anterior two-thirds of the tongue are found in the fungiform papillae, and are innervated by the chorda tympani branch of the facial nerve (cranial nerve VII). On the palate, taste receptors are innervated by another branch of the facial nerve, the major superficial petrosal nerve.

Taste is often difficult to differentiate from the sense of smell, and the combination of these two sensory experiences is commonly given the composite label “flavour”. With respect to aroma, volatile molecules that are released during chewing and oral processing travel up the nasopharynx, producing retronasal stimulation of receptors in the olfactory epithelium of the upper part of the nasal cavity. This stimulation leads to the transmission of sensory information to the olfactory bulb of cranial nerve I (olfactory nerve). In addition to taste and smell, another sensory aspect of the bolus that may be perceived as part of flavour is chemosensation. Chemesthesis refers to activation of ion receptors for the trigeminal nerve (cranial nerve V, maxillary branch), which are housed in the epithelial cells of the oral cavity [(22)(23)]. Chemical aspects of the bolus may include acidity related to sourness, thermal characteristics related to compounds such as capcaisin, piperine or menthol, and fizziness related to carbonation [(24)].

Tactile aspects of the bolus such as volume and consistency are detected by mechanoreceptors of the trigeminal nerve in the mouth. The afferent pathways of these different cranial nerves communicate information about the sensory characteristics of the bolus to cortical sensory areas via the thalamus. Transient Potential Ion Channel Receptors (TRP), especially subtypes TRPV1, TRPA1 and TRPM8, are thought to be particularly important for integrating somatosensory information during this process [25]. Neuroimaging studies show that volitional swallowing is represented in multiple cortical regions bilaterally and asymmetrically [12]. This asymmetrical interhemispheric representation for swallowing is independent of handedness [12][26][27]. Cortical areas that are important for swallowing include the precentral and inferior frontal gyri as well as other regions adjacent to the Sylvian fissure and the lateral and precentral cortex [9]. From these regions, information descends via corticobulbar pathways to the swallowing control centers in the brainstem [12]. This neural architecture provides the primary mechanism by which sensory information about a bolus can be used to modulate the motor aspects of swallowing [28].

1.1.2 Oral Propulsive Phase

The oral propulsive phase, which follows the oral preparatory phase, is also voluntary, and its main function is transport of the bolus to the oropharynx. With solid foods, particles of moistened food are collected by the tongue and transported through the faucial pillars to collect in the vallecular space in the upper pharynx[13]. With liquids, the anterior part of the tongue presses against the hard palate, squeezing the bolus towards the back of the oral cavity. When the head of the liquid bolus arrives at the glossopalatal junction, the soft palate rises, allowing the bolus to flow into the pharynx [14][15][16][29].

As the bolus moves into the posterior portion of the mouth, it passes both the sulcus terminalis of the tongue and the junction between the hard and soft palates. These anatomical boundaries represent important transition points in terms of sensation. In the posterior third of the tongue, taste receptors are located in the foliate and circumvallate papillae, which are innervated primarily by the glossopharyngeal nerve (cranial nerve IX). Receptors on the posterior pharyngeal wall are innervated by the vagal nerve (cranial nerve X). Together, the sensory fibers of cranial nerves IX and X form the pharyngeal plexus. Afferent information detected by these receptors is transmitted both to cortical areas and directly to the nucleus tractus solitarius in the medulla.

1.1.3 Pharyngeal phase

In order for a liquid bolus to move into the pharynx, the soft palate elevates, creating an opening of the glossopalatal junction. Simultaneously, the lateral walls of the nasopharynx move medially to create a seal at the velopharyngeal junction that will prevent the regurgitation of material into the nasal cavity. These events mark the end of the oral propulsive phase and the beginning of the pharyngeal phase of swallowing, which is generally considered to be involuntary, meaning that it cannot be interrupted once initiated. The motor components of the pharyngeal phase are sometimes referred to as the oropharyngeal motor response (OPMR) and involve movement of the hyolaryngeal complex to protect the airway. Contraction of the suprahyoid muscles and the longitudinal muscles of the pharynx move the hyoid and larynx move upwards and forwards, thereby moving the entrance to the airway under the base of the tongue, out of the path of the alimentary bolus. As the bolus moves downwards, it pushes the leaf of the epiglottis downwards, creating a mechanical barrier that prevents food from entering the larynx. Beneath this layer of protection, the arytenoid cartilages move forward to contact the base of the epiglottis, thereby closing the laryngeal vestibule (LV), and the true vocal folds adduct to prevent material from travelling into the trachea. Contraction of the suprahyoid and longitudinal pharyngeal muscles also facilitates shortening of the pharynx and places biomechanical traction on the upper esophageal sphincter (UES) to assist with opening, thereby facilitating passage of the bolus into the esophagus [4][5][30].

At a neurophysiological level, the patterned behaviours involved in initiating the OPMR are thought to be under the control of a central pattern generator located in the medulla oblongata, and specifically involving sensory ganglia, interneurons and motor nuclei in the nucleus tractus solitarius (NTS), the nucleus ambiguus, and adjacent reticular formation [9]. Sensory receptors for the internal branch of the superior laryngeal nerve (cranial nerve X) can be found on the epiglottis and in the laryngeal vestibule [21]. Excitation of these receptors together with the pharyngeal branch of the glossopharyngeal nerve (cranial nerve IX) influences the frequency of rhythmic neuronal firing in the dorsal NTS (i.e., the Dorsal Swallowing Group or DSG). The synaptic response of these neurons has been shown to have a very short and stable latency (1-2 ms), indicating a monosynaptic connection with the afferent neurons [2]. From here, the swallowing signal travels via the Ventral Swallowing

Group (VSG) on the ventrolateral side of the medulla, to the nucleus ambiguus. Several pulses are required to initiate the response of the VSG (7-12 ms), suggesting a polysynaptic pathway [2] involving activation of the VSG neurons by the DSG neurons. When the necessary stimulation threshold is reached, the interneurons of the VSG are thought to be responsible for distributing the swallowing motor command to the different motor nuclei including the dorsal motor nucleus of the vagus nerve and the hypoglossal nucleus (cranial nerve XII) [2].

As the bolus travels downwards through the pharynx, a top-down sequence of muscle contraction can be observed in the pharyngeal constrictor muscles. This pharyngeal stripping wave chases the bolus downwards through the pharynx. The cricopharyngeus muscle forms part of the upper esophageal sphincter (UES) and is usually contracted at rest. The neural command to this muscle must be temporarily inhibited to lower the contraction, so that the traction forces that are placed on the sphincter by hyolaryngeal excursion can facilitate opening, allowing the bolus to pass into the cervical esophagus [31].

1.1.4. Esophageal phase

The esophageal phase is the final phase of swallowing and is involuntary. This phase is controlled by the enteric nervous system and is characterized by peristaltic contraction of the smooth muscle walls of the esophagus, which help to carry the bolus down towards the lower esophageal sphincter and stomach [15] [16] [32].

1.2 Aging in Brazil and around the world

Population aging is one of humankind's greatest triumphs. However, it is also one of the greatest challenges that we face, because it generates an increase in social and economic demands in all nations. Aging is a natural process, characterized by changes in physical, psychological and social function. These changes impact both the survival of each individual and their quality of life (33)(34).

According to the World Health Organization (WHO) (2002)[35], the term “elderly” is usually defined based on chronological age; however, in functional terms, the age at which people can be considered elderly differs according to the level of development and socioeconomic status of the country. In developed countries, the

WHO considers elderly people to be those aged 65 years or older, and in under developing countries, people aged 60 or older are considered elderly(35). In Brazil, use of the age of 60 years to classify a person as elderly is in accordance with the National Elderly Policy of 1994 (NEP) (36) (Law 8,842) and the Elderly Statute (37) of 2003 (Law No. 10,741).

Brazil, like most developed countries, has experienced a rapid and growing increase in the number of elderly people in recent decades. Unfortunately, however, Brazil does not yet have resources either planned or available to meet the demands of this population. Developing plans for this population to remain healthy and active, along with measures to monitor function, is imperative (33)(34)(35).

It is estimated that between 1970 and 2025 there will have been an increase of 223% (approximately 694 million) in the number of elderly people worldwide. By 2025, it is expected that there will be 1.2 billion elderly people and, by 2050, 2 billion people over the age of 60, with 70-80% of these individuals living in developing countries (35)(38). Data from the Brazilian National Census showed that in 2010, of the 190 million inhabitants in the country, 20.6 million were approximately 60 years old and 3 million around 80 years old. Estimates regarding demographic evolution of the Brazilian population (U. S. Census Bureau) suggest that by 2025 there will be approximately 32 million elderly people in Brazil. This number will rank Brazil sixth in the world with respect to the number of elderly people (35)(39).

A major problem associated with the accelerated growth of the elderly population in developing countries is that socio-economic growth is not at the same pace as that seen in developed countries. While people in developed countries have typically achieved economic stability before they reach old age, this is not the case in developing countries (40). According to Garcez-Leme & Leme (2014) (41), the Brazilian Public Health System (SUS) spends approximately US$ 2 billion annually on the hospitalization of elderly people; this figure represents slightly less than one third of healthcare expenditures for total population. Taking these data and projections into account, there are reasons to be concerned about the availability of adequate resources and sufficiently qualified professionals to meet the needs of older persons in Brazil.

If we take into account projections regarding growth of the world's elderly population, it is clear that the prevalence of swallowing difficulties is likely to increase, due both to aging and to comorbidities. The number of older individuals in Brazil who will present some difficulty to feed themselves is likely to grow exponentially.

Establishing a clearer understanding of the effects of aging on swallowing function will allow us to plan better to meet the needs of this population in the future, both with respect to prevention and treatment.

1.3 Swallowing in the elderly population and timing measures

Understanding the nature of swallowing in healthy people is a prerequisite for determining the nature and extent of swallowing impairment (dysphagia) in people with swallowing problems(42). Normal age-related changes in swallowing are called *presbyphagia*, and include changes that occur as a consequence of age-related physiological degeneration of nerve and muscle fibers (43). Additionally, changes may be seen in sensory function or in the coordination and timing of muscle contraction.

Given that the oropharynx is comprised of skeletal and striated muscles, it is reasonable to expect age-related atrophy and loss of strength in these muscles (44). Among the changes expected with health aging is a decline in tongue strength (45) (46). Older adults are also reported to need a longer time to build peak tongue pressure(47). The literature suggests that older adults with tongue weakness are at increased risk both for impaired swallowing safety in the form of aspiration (i.e. entry of material into the airway) (48) and for reduced efficiency of swallowing, which can present in the form of oral residue, pharyngeal residue and fractional or piecemeal swallowing (4)(28). Slower bolus velocities (<10cm/s) have also been observed in older adults and attributed to weak propulsive lingual force (<0.14 mJ) (49).

Interestingly, healthy older adults only demonstrate reduced tongue strength in the context of maximum isometric tasks; differences are not seen in the submaximal effort context of swallowing (47)(50). This is often interpreted to reflect a reduction in functional reserve in the elderly. There is some evidence to suggest that the head and neck musculature loses bulk and strength in a manner similar to that seen in sarcopenia in the limb muscles, and that older adults with malnutrition and sarcopenia are at greater risk (51)(52)(53). In particular, it is important to understand whether age-related losses in tongue or other swallowing muscle strength lead to a reduction in functional reserve, which might place older people at a disadvantage in terms of their ability to maintain functional swallowing in the face of injury, decompensation or disease [47]. Elderly people with a frail phenotype [54] are thought to be the most susceptible and vulnerable to developing swallowing impairment. These individuals have a high prevalence of swallowing impairment compared to robust elderly patients in the community; risk factors including functional disability, poor nutritional status, sarcopenia or muscle weakness, and other comorbidities are thought to contribute to this situation [55][56].

As previously discussed, the integrity of the swallowing mechanism also relies heavily on afferent input to the cortex and the brainstem. The availability of sensory information and feedback during swallowing is of key importance for triggering and modulating the oropharyngeal swallow response. However, sensory changes are also thought to occur as part of healthy aging and, in particular, a progressive loss of sensitivity of key areas in the pharynx and larynx has been described [57] [58]. An age-related reduction occurs in the number of myelinated nerve fibers of the superior laryngeal nerve [57][58][59][60]. This is thought to contribute to oropharyngeal dysphagia and impaired safety of swallow [61] [62] [63] [64].

Safe and efficient swallowing involves precise timing and coordinated contraction of at least 25 bilateral pairs of muscles in the upper aerodigestive tract [44]. Videofluoroscopy is a standard instrumental assessment used to evaluate the safety and efficiency of swallowing, which also provides the opportunity to measure the timing of swallowing events. Typically, the primary focus of a videofluoroscopy is on characterizing swallowing function, and specifically on confirm the presence/absence and severity of penetration-aspiration, as defined by the 8-point Penetration- Aspiration scale [65]. It is less common for more detailed analyses of pathophysiology to be made, such as measurements of timing.

A recent review and meta-analysis by Namasivayam and colleagues summarizes what is known regarding age related changes in timing measures of swallowing [1][44][66] [67][68][69][70][71][72]. Overall, these authors concluded that the literature does not contain strong evidence to suggest that age influences bolus transit time, however significantly delayed swallow response time and longer durations of UES opening appear to be characteristic of swallowing in healthy older adults [44]. The authors cautioned that many studies of swallow timing are under-powered and/or did not evaluate the entire process of swallowing from the moment the bolus enters the oral cavity to the point when it has completely moved into the esophagus [44]. They point out that the literature contains highly variable results, and differences across studies in the definitions of timing measures, which make it difficult to compare results [44][73][74]. Furthermore, when timing differences have been described, the physiological reasons for such differences have not been discussed, leading to limited understanding of the clinical relevance of the observed differences [74]. These issues should be kept in mind throughout the summary below of possible age-related differences in swallow timing.

Most of the swallow timing studies published, describe the duration of specific swallowing events as duration of laryngeal closure, UES opening and closure or bolus transit time[10][30][42][44] [74][73]. It must be remembered that variations in size of the bolus might influence timing measures. In young healthy people, with 10cc bolus, confidence intervals for commonly reported timing measures are as follows[75]:

- Swallow reaction time (which the authors call stage transition duration, defined as the time interval between the bolus passing the mandible and the onset of the hyoid burst movement): 9-103 ms;
- UES closure duration (UES closure to UES opening): 292-348 ms;
- Laryngeal closure duration (laryngeal closure to laryngeal opening): 434-546 ms;
- Pharyngeal transit time (UES closure to bolus passing mandible): 456-568 ms.

By contrast, some aspects of swallow timing are reported to be altered in the elderly, especially in those with neurogenic diseases (5)(49) (76). Many studies report longer pharyngeal transit time in older subjects in comparison with younger subjects (1)(77)(78)(79)(80), and associate this finding with the general characteristic of slower movement seen in aging (81). For example, Rademaker and colleagues (42) reported that elderly female volunteers presented longer pharyngeal transit time than younger controls, together with longer durations of velopharyngeal closure and UES opening. In older men, using the same methods, the findings included longer pharyngeal delay and a shorter interval between the onset of posterior pharyngeal wall movement and UES opening (71).

Several studies in the literature concur that older adults have a longer overall duration of the OPMR, primarily due to the delayed initiation of the pharyngeal phase (reconfiguration of the airway to digestive path) (49). In addition, the time intervals between opening of the glossopalatal junction and the subsequent events of LVC and UESO are reported to be up to twice as long as that seen in healthy younger volunteers; this represents a risk for aspiration (5)(49). Delayed initiation of the OPMR, with a lower bolus position at onset, and a longer time interval to LVC are thought to be very common reasons for impaired swallowing safety in older adults with neurodegenerative diseases, confusion, dementia and use of some medications (12) (19) (82).

The focus of the analyses in this dissertation is on timing measures in swallowing. Specifically, we believe that by measuring the timing of swallow events, we can gain important insights that will help us to better understand normal swallow physiology and identify the pathophysiology of dysphagia. In particular, we will focus on identifying differences in timing that occur as part of the normal process of healthy aging in comparison to changes that are pathological and part of the presentation of dysphagia.

Justification

2 JUSTIFICATION

Normal aging leads to adaptations in swallowing. Understanding the effect of aging on the swallowing mechanism is extremely important so that we can identify dysphagia and pursue interventions to minimize swallowing difficulties in this population. Eating is a social act in our culture, and any dysfunction that impedes this process directly impacts the quality of life of the elderly, increasing the risk of malnutrition, dehydration and depression.

The focus in this thesis was to perform timing measurements of swallowing to better understand differences between healthy aging and functional swallows in individuals who are thought to have swallowing problems. The term “functional swallows” refers to swallows that are safe and efficient, even when other aspects of those swallows, such as timing, may be abnormal.

Purpose

3 PURPOSE

3.1 Primary objective

To determine whether temporal measures of thin liquid swallowing differ for the following 3 groups:

a) Healthy young adults
b) Healthy older adults
c) Functional swallows (i.e., safe and efficient) collected from adults referred for swallowing assessment due to complaints of dysphagia.

3.2 Secondary objective

To determine whether differences in timing explain the occurrence of transient penetration of material into the laryngeal vestibule (Penetration-Aspiration Scale [PAS] scores of 2) in any of these groups.

Hypotheses

4 HYPOTHESES

Our hypotheses were:

- All parameters related to swallow response, bolus transit, laryngeal vestibule closure and UES function will be longer in the older healthy group in comparison with healthy young adults, and even longer in the older group at risk for dysphagia
- - Older people and older people at risk for dysphagia will have a higher frequency of transient laryngeal penetration (PAS = 2) and longer timing measures when penetration is present

Materials and Methods

5 MATERIALS AND METHODS

5.1 Ethical considerations

This study was approved by the Research Ethics Committee of the Clínical Hospital of Medical School of Ribeirão Preto (Process HCRP No. 8645/2014) (Attached 1) and the University Health Network Research Ethics – Board D, Toronto (16-5752.1) (Attachments 2 and 3). The volunteers signed a free and informed consent form (Attachment 4).

5.2 Population and dataset selection

Data from three different groups of volunteers were included.

5.2.1 Elderly at risk of dysphagia group (EDG)

Data were extracted from a database of videofluoroscopy recordings previously collected at the Toronto Rehabilitation Institute – University Health Network (TRI) for 11 individuals aged 62-87 years old (mean (SD)= 73.1 (9.5) years old), three of whom were female.

All of these individuals were referred to the Swallowing Rehabilitation Research Laboratory at TRI for videofluoroscopic swallowing assessment due to suspected dysphagia. For the purposes of this study, data were selected for inclusion in the dataset provided that the patient demonstrated functional swallowing on all 3 boluses from a series of 3 natural cup sips of thin liquid (20% w/v barium). Functional swallowing was defined as swallowing events with a penetration-aspiration scale score < 3 (65) and residue occupying < 25% of the valleculae and pyriform sinuses. Thus, although these individuals reported symptoms of swallowing difficulty warranting assessment, their thin liquid swallowing was functional without evidence of safety or efficiency concerns. A total of 11 boluses from 6 of the participants in this group displayed PAS scores of 2 (i.e. transient penetration), rather than 1 (no entry of material into the airway).

5.2.2 Healthy young adults group (YHG)

Data were extracted from a database of 10ml thin liquid swallow videofluoroscopy recordings (20% w/v barium) previously collected at the Toronto Rehabilitation Institute (TRI) from 20 individuals, aged between 22 and 45 years old (mean (SD) = 30.5 (5.6) years old), 10 women. None of these individuals reported any history of swallowing complaint, neurological impairment, radiation to the head or neck, or major surgery to the oropharynx or neck. All swallows in this dataset were functional, without evidence of penetration-aspiration scale scores > 2 or residue occupying more than 25% of the valleculae or pyriform sinuses. Data for three 10 ml thin liquid boluses were extracted for each participant.

5.2.3 Healthy elderly group (EHG)

Data were collected prospectively from 17 elderly individuals who consented to undergo a standardized videofluoroscopy. These participants were aged between 61 and 84 years old (mean (SD) = 67.7 (5.6) years old), and included 12 women. None of these participants reported any history of swallowing complaint, neurological impairment, radiation to the head or neck, or major surgery to the oropharynx or neck. To be included, we used the Eating Assessment Tool (EAT-10) (83) as a screening criterion. This instrument suggests presence of possible swallow impairment if the total score is 3 or greater. None of the participants in this group presented scores higher than 2 (Table 1). Each participant swallowed three 10 ml boluses of thin liquid barium (20% w/v) prepared by diluting Bariogel 100% barium sulfate (Laboratório Cristália, Itapira, SP, Brazil) in a ratio of 1 part barium to 6.67 parts water. Videofluoroscopy recordings were acquired in the lateral plane at 30 frames per second (Arcomax Phillips model BV 300, Veenpluis, The Netherlands). A total of 6 boluses from 3 of the participants in this dataset displayed PAS scores higher than 1. One participant displayed a PAS score of 3 on all three boluses. A second participant had PAS scores of 1, 2 and 3 across the three boluses. And a third participant had one PAS score of 2 on their second thin bolus.

Table 1 - EAT-10 results for healthy elderly group.

Participant	EAT-10										
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Total
1	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	1	1	0	2
3	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0	0	0
13	0	0	0	0	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0	0	0
16	0	0	0	0	0	0	0	0	0	0	0
17	0	0	0	0	0	0	0	1	0	0	1

5.3 Videofluoroscopy

5.3.1 Data acquisition

For the videofluoroscopies, the volunteers were seated in a chair with no support for the arms. The fluoroscopic image was defined anteriorly by the lips, superiorly by the hard palate, posteriorly by the posterior wall of the pharynx and inferiorly by the 7th cervical vertebra.

Low concentration thin liquid barium (20% w/v) was used as the contrast stimulus. Boluses (10 ml) were offered in a disposable cup and swallowed in triplicate. Participants were instructed to swallow naturally; no cue or command to swallow was given.

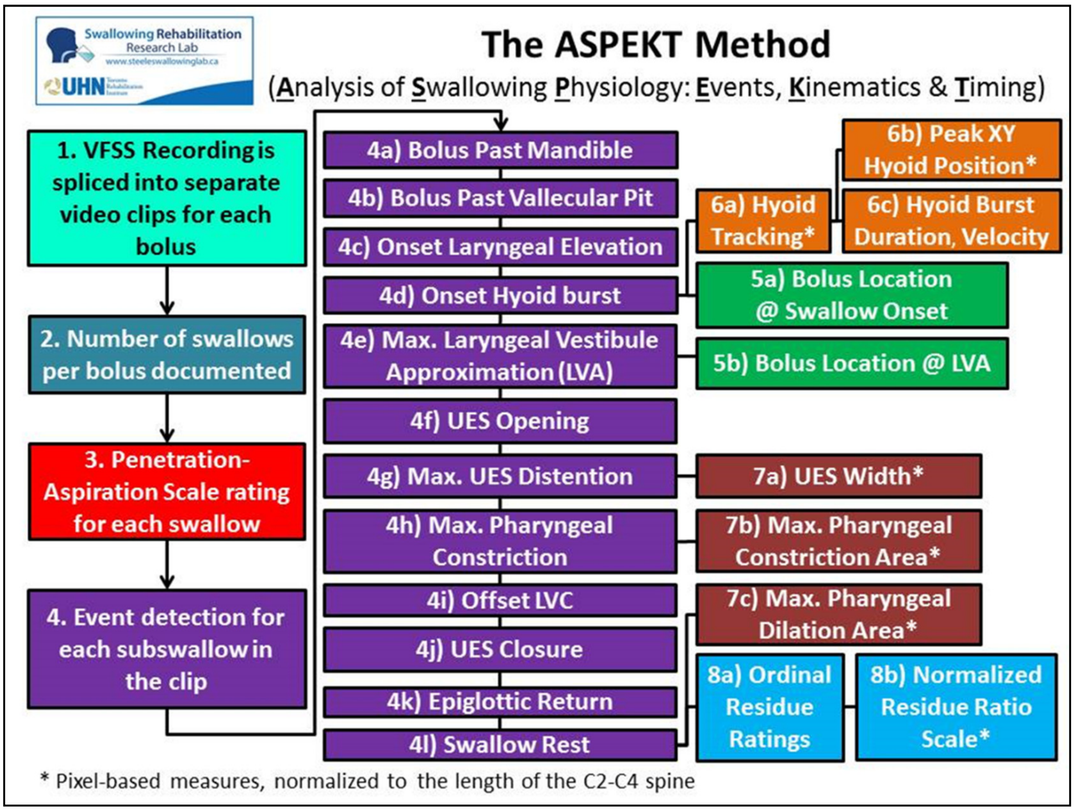
5.3.2 Image preparation

After the data collection, the videofluoroscopy recordings were spliced into shorter bolus length files for analysis. Recordings were imported into ImageJ software for frame by frame review. A standard operating procedure for analysis was used (the ASPEKT method, described below). All ratings were performed in duplicate by two independent raters, who were blind to each other's ratings. All raters received 30 hours of training in the rating methods and demonstrated strong agreement with each other on a training set before proceeding with the rating for this study. An excel file was used to organize all data collected.

5.3.3 The ASPEKT Method

The ASPEKT Method was developed by Professor Catriona Steele, director of the Swallowing Rehabilitation Research Laboratory at the Toronto Rehabilitation Institute – University Health Network. It is a standardized operating procedure for analysis of videofluoroscopy recordings, and is performed in a stepwise fashion, as illustrated in Figure 1 (below). Clear operational definitions are also specified in the method, with the goal of achieving high reliability both within and across raters.

Figure 1 - Flowchart of the ASPEKT method (provided by Dr Steele).



As established by the ASPEKT method, after the videos were spliced into clips per bolus, the number of swallows for each bolus was counted and each swallow was classified into type, as follows:

- Single swallow: the entire bolus crosses the ramus of the mandible in one swallow. This can be followed by a clean-up swallow (where no new material crosses the ramus); however, if new material eventually crosses the ramus on a subsequent swallow, it is considered a piecemeal swallow.
- Piecemeal swallow (either first or subsequent): if the bolus crosses the ramus of the mandible across multiple swallows, the first and subsequent swallows are all considered "piecemeal". Note: the amount of material crossing the ramus of the mandible may be very small but still considered a piecemeal swallow.
- Clean-up swallow: material being swallowed comes from the pharynx only - no new material crosses the ramus of the mandible.
- Attempt (s): unsuccessful swallow (s), defined as pharyngeal constriction with visible hyolaryngeal elevation, or obvious volitional elevation of the larynx in effort to initiate a swallow. The UES does not open despite effort.

Swallowing safety for each subswallow was then rated, according to the 8-point Penetration- Aspiration scale (PAS) [65]:

- Level 1: Material does not enter airway
- Level 2: Material enters the airway, remains above the vocal folds, and is ejected from the airway
- Level 3: Material enters the airway, remains above the vocal folds, and is not ejected from the airway
- Level 4: Material enters the airway, contacts the vocal folds, and is ejected from the airway
- Level 5: Material enters the airway, contacts the vocal folds, and is not ejected from the airway
- Level 6: Material enters the airway, passes below the vocal folds, and is ejected into the larynx or out of the airway
- Level 7: Material enters the airway, passes below the vocal folds, and is not ejected from the trachea despite effort
- Level 8: Material enters the airway, passes below the vocal folds, and no

effort is made to eject (silent aspiration).

The frame numbers for any penetration events were recorded. The amount of bolus invasion was recorded as being a trace or more than trace.

Following the flowchart, the next step in the ASPEKT method involves documenting the frame number at which 12 key events occurred. These are shown in the purple boxes in Figure 1. For the purposes of this particular study, 7 of these events were of particular interest:

1. Bolus passing mandible (BPM): Recorded the first frame where the leading edge of the bolus touches or crosses the shadow of the ramus of mandible. In cases of premature spill, the first entry of bolus material into the pharynx has been counted as the BPM frame. If there is a double mandible shadow, the lower edge of the more superior ramus was used as the landmark.
2. Onset of hyoid burst: Recorded the first anterior-superior 'jump' of the hyoid that is associated with a swallow (or swallow attempt). This was the moment where the hyoid appeared to 'take off' or 'burst'; small movements around the starting position that occurred prior to this burst were not counted. In the case of swallow attempts, the first hyoid burst attempt frame was marked on the first event in the sequence.
3. Laryngeal vestibule closure (LVC) (or maximum approximation): The first frame where there was maximum approximation of the arytenoids to the laryngeal surface of the epiglottis. Complete closure of the laryngeal vestibule (i.e. seal between epiglottis and arytenoids leaving no visible airspace) may or may not have been present.
4. Upper esophageal sphincter (UES) opening: The first frame where the leading edge of the bolus (or in rare cases air) passes through the UES. The UES is a narrow segment or region that typically lies between C4-C6 during a swallow is usually marked as the location of the sphincter (as per Kendall & Leonard)[84]. In the ASPEKT method, the criteria recognize that the UES moves superiorly during the swallow. Therefore, the narrowest portion may be located above C4. The laryngeal air column may be used as a guide to decide where the location of the UES is during pharyngeal shortening.
5. Laryngeal vestibule opening (LVO): The first frame where there was a visible opening (white space) of the laryngeal vestibule. This required some

separation of the tissues or of the arytenoids from the under surface of the epiglottis. Complete opening was not required. The leaf of the epiglottis may still be in a downward position. If LVC had been marked as incomplete, this variable was marked as "not applicable".

6. Maximum pharyngeal constriction (MPC): The earliest frame of maximum pharyngeal constriction was chosen (i.e., the first frame showing the smallest amount of unobliterated space in the pharynx). This event typically occurred between the UES opening and the LVO. The raters were instructed to choose a frame before the upper pharynx began to relax, and before the laryngeal air column began to descend.
7. UES closure: The first frame where the UES achieved closure behind the bolus tail was chosen. This did not require closure of the entire UES segment, simply closure at a single point along the segment.

The ASPEKT method continues with additional steps for measuring residue severity, hyoid movement and pharyngeal constriction using pixel-based tracing methods. The location of the bolus at the frames of hyoid burst onset and laryngeal vestibule closure are also recorded. These steps were not part of the current study

5.3.4 Consensus

Prior to any analysis, the rating data were reviewed for agreement across the two raters. Any of the following discrepancies in ratings between the two raters resulted in subsequent review of the bolus recording at a consensus meeting, in order to resolve the discrepancy:

- Any difference in penetration-aspiration score
- Any discrepancy in whether laryngeal vestibule closure was complete or incomplete
- Differences in frame numbers > 5 frames for the events of interest. (In the event of differences < 5 frames, the earliest of the two frames was chosen as the frame of record).

5.3.5. Timing Parameters

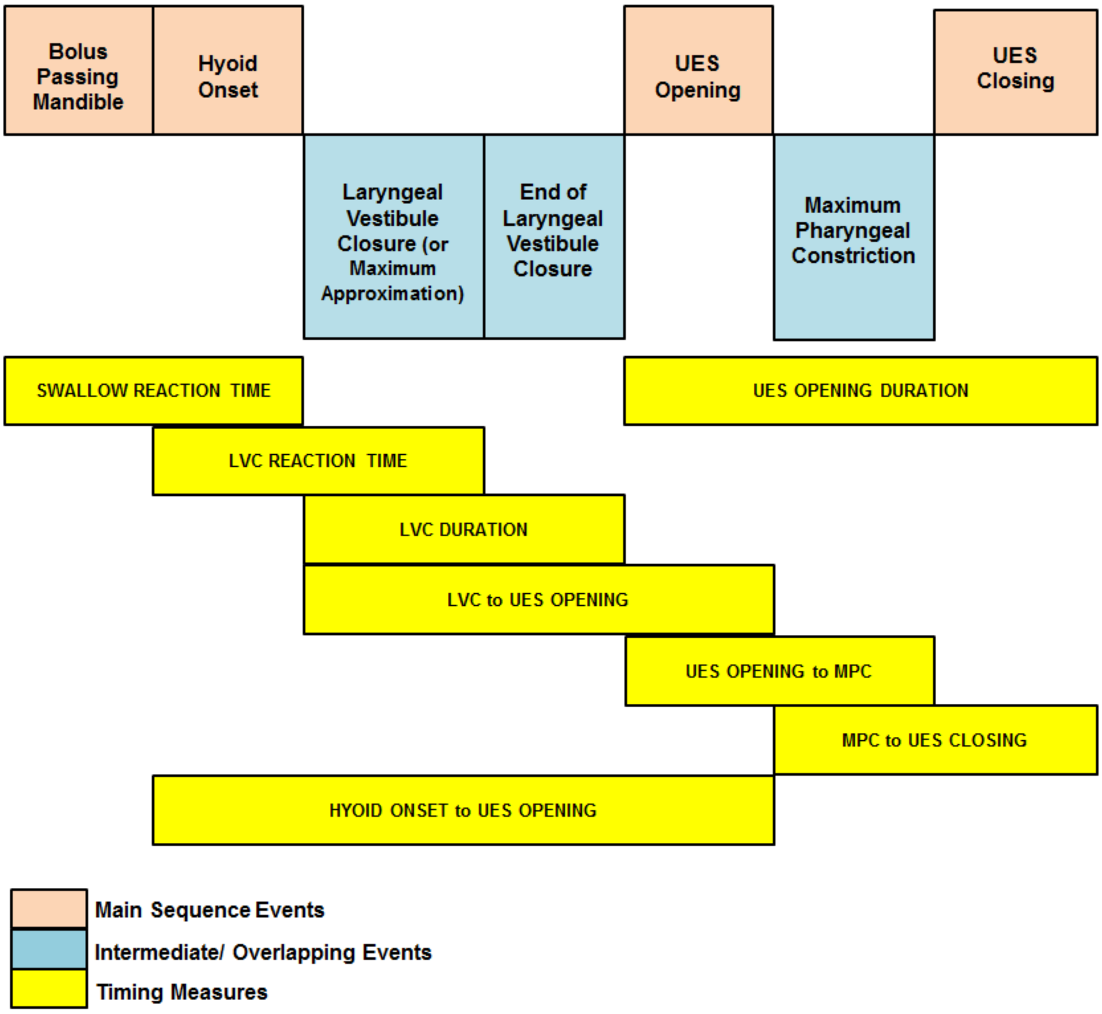
Once the frame numbers for each of the events of interest were confirmed, timing parameters were derived in milliseconds. Figure 2 illustrates the timing parameters of interest, which were defined as follows:

- Swallow Reaction Time : the interval between bolus passing mandible and onset of the hyoid burst
- Hyoid Onset to UES Opening: the interval between onset of the hyoid burst and opening of the UES
- UES opening duration: the interval between UES opening and UES closure. This measure can be further broken down into two subcomponents:
  - UES opening to MPC: the interval between UES opening and maximum pharyngeal constriction
  - MPC to UES closure: the interval between MPC and UES closure.

In addition to these parameters, three additional measures capturing the timing and duration of laryngeal vestibule closure were calculated:

- LVC reaction time: the interval between onset of the hyoid burst and laryngeal vestibule closure (or maximum approximation)
- LVC to UES opening : the interval between LVC and UES opening
- Laryngeal closure duration: the interval between laryngeal vestibule closure and laryngeal vestibule opening

Figure 2 - Study timing parameters.



5.4 Statistical analysis

All statistics analyses were conducted using IBM SPSS Statistics, version 21. Linear mixed model repeated measures ANOVA were performed in order to analyze the timing parameters and PAS effect. All *p* values <0.05 were considered significant. Data were described using mean, standard deviation (SD), and 95% confidence interval (CI).

Results

6. RESULTS

6.1 Healthy young adults vs healthy elderly group

In the comparison between healthy young adults and the healthy elderly group, we found that the majority of the timing measures of interest differed between groups:

- Swallow reaction time and upper esophageal sphincter opening duration were significantly longer in the healthy older group.
- The interval between hyoid onset and upper esophageal sphincter opening was significantly shorter in the healthy older group. Given the previous finding of longer swallow reaction times, this finding is likely to reflect later onset of hyoid movement.
- The interval between upper esophageal sphincter opening and maximum pharyngeal constriction was significantly longer in the healthy older group.
- The interval between laryngeal vestibule closure and upper esophageal sphincter opening was significantly longer in the healthy older group, and was negative, meaning that laryngeal vestibule closure occurred after upper esophageal sphincter opening. This timing pattern was opposite to that seen in the healthy younger subjects.
- There were no differences in laryngeal vestibule closure reaction time, laryngeal closure duration and the interval between maximum pharyngeal constriction to upper esophageal sphincter closure.

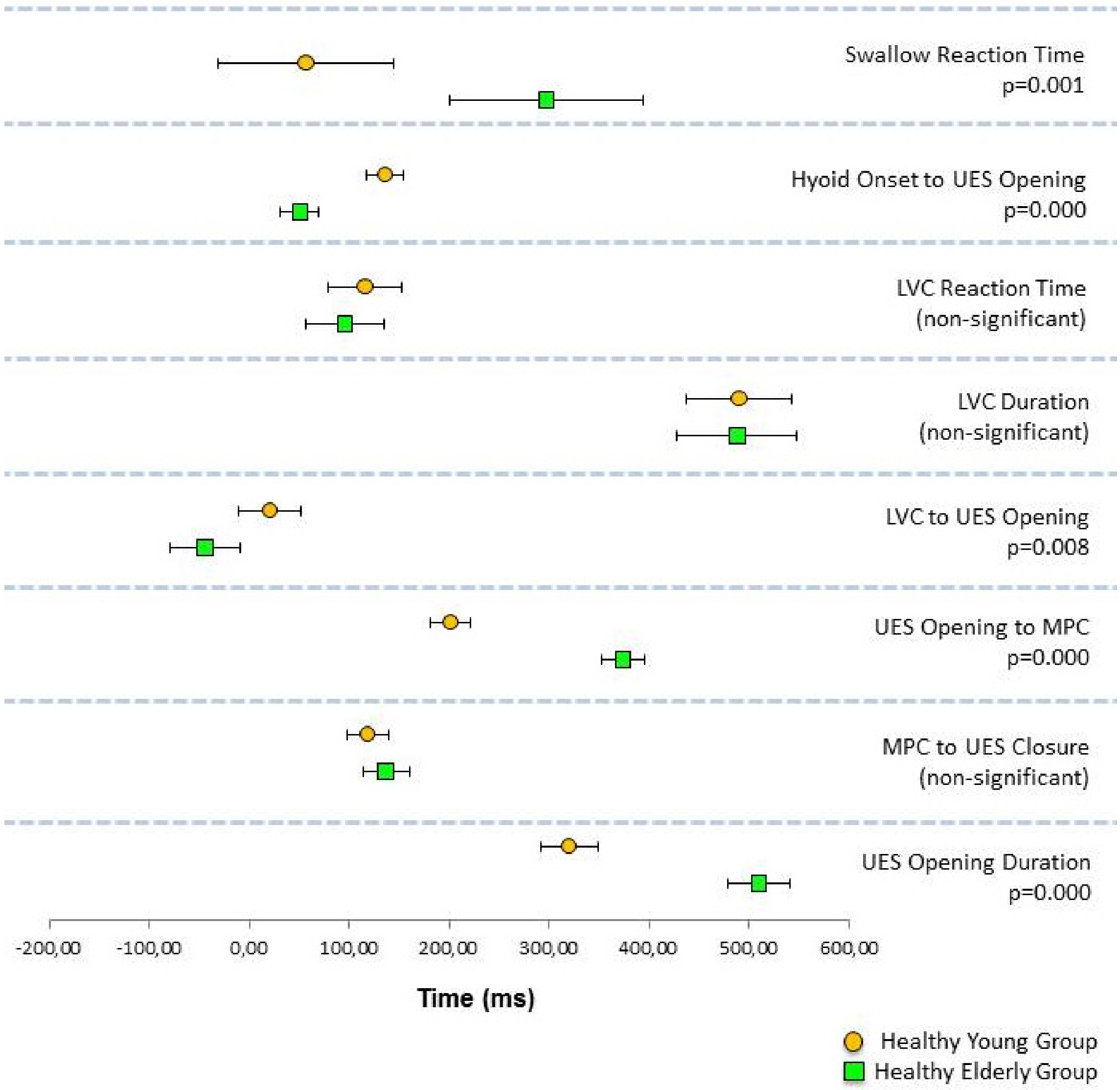
  All results are demonstrated in Table 2 and Figure 3.

Table 2 - Differences in timing measures between healthy young adults versus healthy older adults.

		Mean	SD	LCI	UCI	p-value
Swallow Reaction Time (ms)	Healthy young adults	56.18	158.14	-32.35	144.72	0.001
	Healthy older adults	296.71	326.12	199.76	393.65	
Hyoid onset to UESO (ms)	Healthy young adults	135.53	52.74	117.70	153.36	0.000
	Healthy older adults	50.41	45.41	30.94	69.88	
LVCRT (ms)	Healthy young adults	115.60	96.25	79.47	151.73	0.442
	Healthy older adults	95.15	87.21	55.81	134.49	
Laryngeal Closure Duration (ms)	Healthy young adults	489.83	138.01	437.08	542.58	0.961
	Healthy older adults	487.91	124.35	427.95	547.87	
LVC to UES Opening (ms)	Healthy young adults	20.07	76.97	-11.53	51.67	0.008
	Healthy older adults	-44.42	94.81	-78.88	-9.96	
UES opening to MPC (ms)	Healthy young adults	201.32	51.51	181.41	221.23	0.000
	Healthy older adults	373.36	52.62	351.65	395.07	
MPCtoUESC	Healthy young adults	118.38	62.15	97.13	139.64	0.250
	Healthy older adults	136.50	51.93	113.30	159.71	
UES opening duration (ms)	Healthy young adults	319,80	68.75	290.90	348.70	0.000
	Healthy older adults	509.59	77.58	478.12	541.06	

*LCI = 95% Confidence Interval Lower Boundary
**UCI = 95% Confidence Interval Upper Boundary

Figure 3 - Differences in timing measures between healthy young adults versus healthy older adults.



6.2 Healthy elderly vs elderly at risk of dysphagia group

In the comparison between the healthy elderly group and the elderly group at risk of dysphagia, we found the following timing differences:

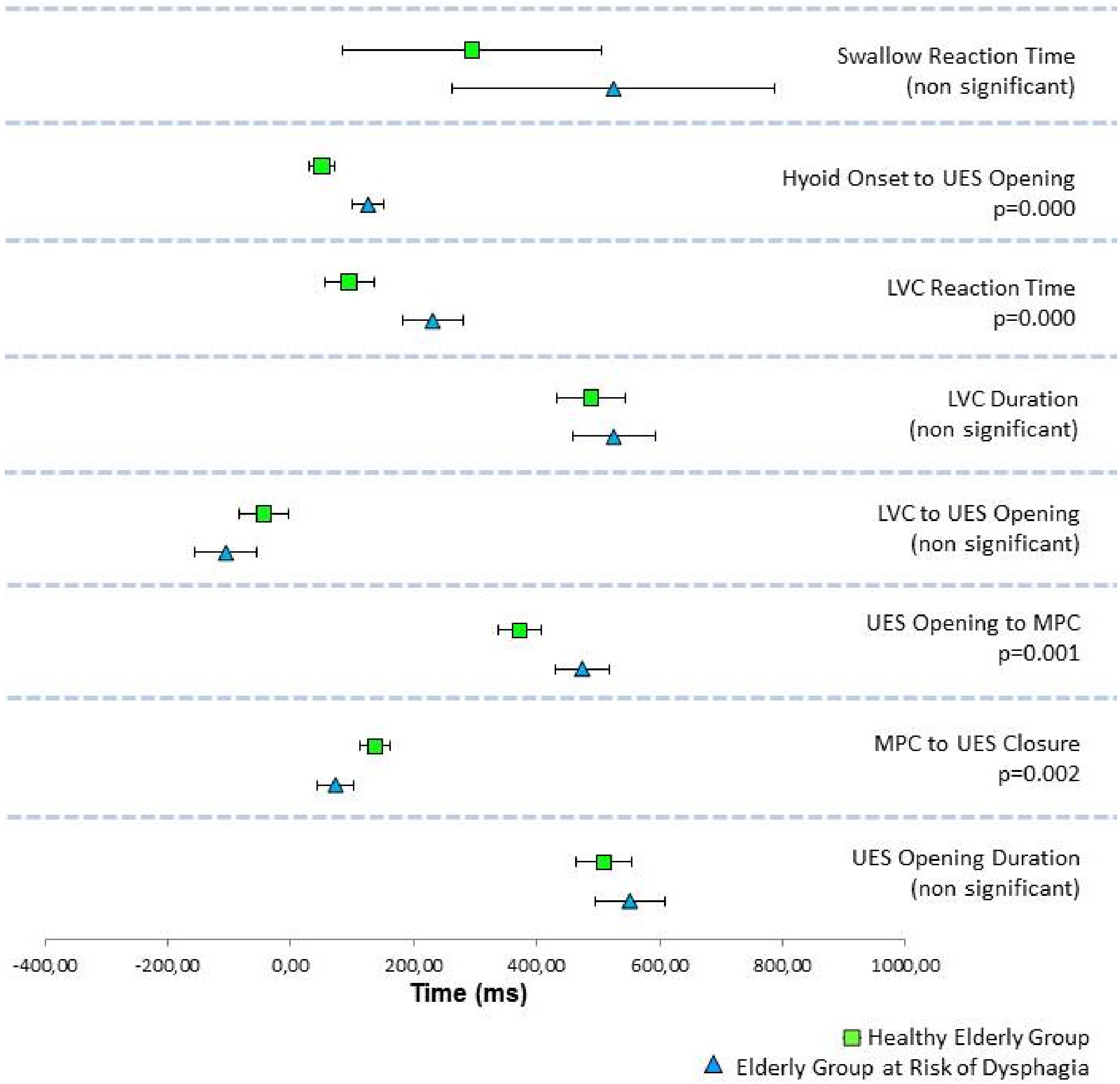
- The interval between hyoid onset and upper esophageal sphincter opening and laryngeal vestibule closure reaction time were both significantly longer in the elderly group at risk of dysphagia.
- The interval between laryngeal vestibule closure and upper esophageal sphincter opening was longer in the elderly group at risk of dysphagia, but this finding failed to reach statistical significance ($p=0.060$). In both groups this timing measure had a negative value indicating that laryngeal vestibule closure occurred after upper esophageal opening; however, laryngeal vestibule closure was later in the elderly group at risk of dysphagia.
- The interval between upper esophageal sphincter opening and maximum pharyngeal constriction was significantly longer in the group at risk of dysphagia.
- The interval between maximum pharyngeal constriction and upper esophageal sphincter closure was significantly shorter in the group at risk of dysphagia.
- There were no significant differences between these groups in swallow reaction time, laryngeal closure duration, or upper esophageal sphincter opening duration.

These results are shown in Table 3 and Figure 4.

Table 3 - Differences in timing measures between healthy older adults versus older adults at risk of dysphagia.

		Mean	SD	LCI	UCI	p-value
Swallow Reaction Time (ms)	Healthy older adults	295.39	326.15	84.82	505.95	0.170
	Older adults referred for swallowing assessment	525.05	560.97	261.73	788.36	
Hyoid onset to UESO (ms)	Healthy older adults	50.25	45.41	29.74	70.77	0.000
	Older adults referred for swallowing assessment	125.51	70.41	100.06	150.97	
LVCRT (ms)	Healthy older adults	94.65	87.21	54.63	134.66	0.000
	Older adults referred for swallowing assessment	230.49	146.13	181.19	279.78	
Laryngeal Closure Duration (ms)	Healthy older adults	488.82	124.35	433.78	543.85	0.391
	Older adults referred for swallowing assessment	525.42	169.72	458.46	592.38	
LVC to UES Opening (ms)	Healthy older adults	-44.33	94.81	-84.66	-4.01	0.060
	Older adults referred for swallowing assessment	-105.80	160.39	-155.79	-55.81	
UES opening to MPC (ms)	Healthy older adults	373.19	52.62	338.20	408.19	0.001
	Older adults referred for swallowing assessment	474.12	102.70	430.65	517.58	
MPCtoUESC (ms)	Healthy older adults	136.54	51.93	112.00	161.09	0.002
	Older adults referred for swallowing assessment	72.70	74.35	42.42	102.98	
UES opening duration (ms)	Healthy older adults	509.42	77.59	463.58	555.26	0.248
	Older adults referred for swallowing assessment	551.48	117.93	494.53	608.53	

Figure 4 - Differences in timing measures between healthy older adults versus older adults at risk of dysphagia.



6.3 Penetration-Aspiration Scale Scores

In total, we analyzed 144 swallows. Among these, 23 swallows (i.e.16%) involved transient penetration (i.e. PAS scores of 2). These events were distributed as follows: in the healthy young group, 6/60 swallows (i.e. 10%) with penetration were found; another 6/51 (i.e. 11.7%) penetration events were found in the healthy elderly group; and finally, 11/33 (i.e. 33%) penetration events were observed in the elderly at risk of dysphagia group. As mentioned earlier, we hypothesized that swallows on which transient penetration occurred would be characterized by longer timing measures compared to swallows with penetration-aspiration scale scores of 1.

6.4 Differences in timing measures related to Penetration-Aspiration Scale score in the healthy young and healthy elderly group

The analysis found no significant interactions between sample and PAS score, but showed a trend or main effect of PAS score on two timing measures as follows:

- Laryngeal vestibule closure reaction time was longer in cases of transient penetration but this finding failed to reach statistical significance (p=0.060).
- The interval between laryngeal vestibule closure and upper esophageal sphincter opening was significantly longer and more negative when penetration was observed (p=0.003). This shows later closure of the laryngeal vestibule relative to UES opening when penetration occurs.

In addition, there was a main effect of sample (as previously described), with significantly longer swallow reaction time and UES opening duration, significantly longer intervals from LVC to UES opening and from UES opening to MPC, and a significantly shorter interval from hyoid onset to UESO in the older participants.

These results are illustrated in Table 4 and Figures 5 and 6.

Table 4 - Effect of PAS score on timing measures in the healthy young group and healthy elderly group.

		Mean	SD	LCI	UCI	p-value
Swallow Reaction Time (ms)	PAS 1	161.82	267.34	95.07	228.56	0.213
	PAS 2 or higher	276.10	288.37	102.12	450.08	
Hyoid onset to UESO (ms)	PAS 1	95.96	64.02	82.34	109.58	0.178
	PAS 2 or higher	70.69	76.07	35.07	106.30	
LVCRT (ms)	PAS 1	97.9	92.50	70.73	125.07	0.060
	PAS 2 or higher	164.85	63.68	97.05	232.65	
Laryngeal Closure Duration (ms)	PAS 1	488.45	124.50	446.97	529.94	0.865
	PAS 2 or higher	479.04	190.55	373.57	584.52	
LVC to UES Opening (ms)	PAS 1	-1.54	84.20	-23.68	20.60	0.003
	PAS 2 or higher	-94.97	97.73	-152.29	-37.65	
UES opening to MPC (ms)	PAS 1	288.04	99.26	272.32	303.77	0.749
	PAS 2 or higher	281.37	110.95	241.26	321.48	
MPC to UESC (ms)	PAS 1	125.76	58.85	109.63	141.88	0.555
	PAS 2 or higher	138.75	51.94	96.68	180.82	
UES opening duration (ms)	PAS 1	414.49	111.14	392.28	436.70	0.990
	PAS 2 or higher	414.55	158.20	359.11	469.97	

Figure 5 - Effect of PAS score on timing measures in the healthy young group vs healthy elderly group.

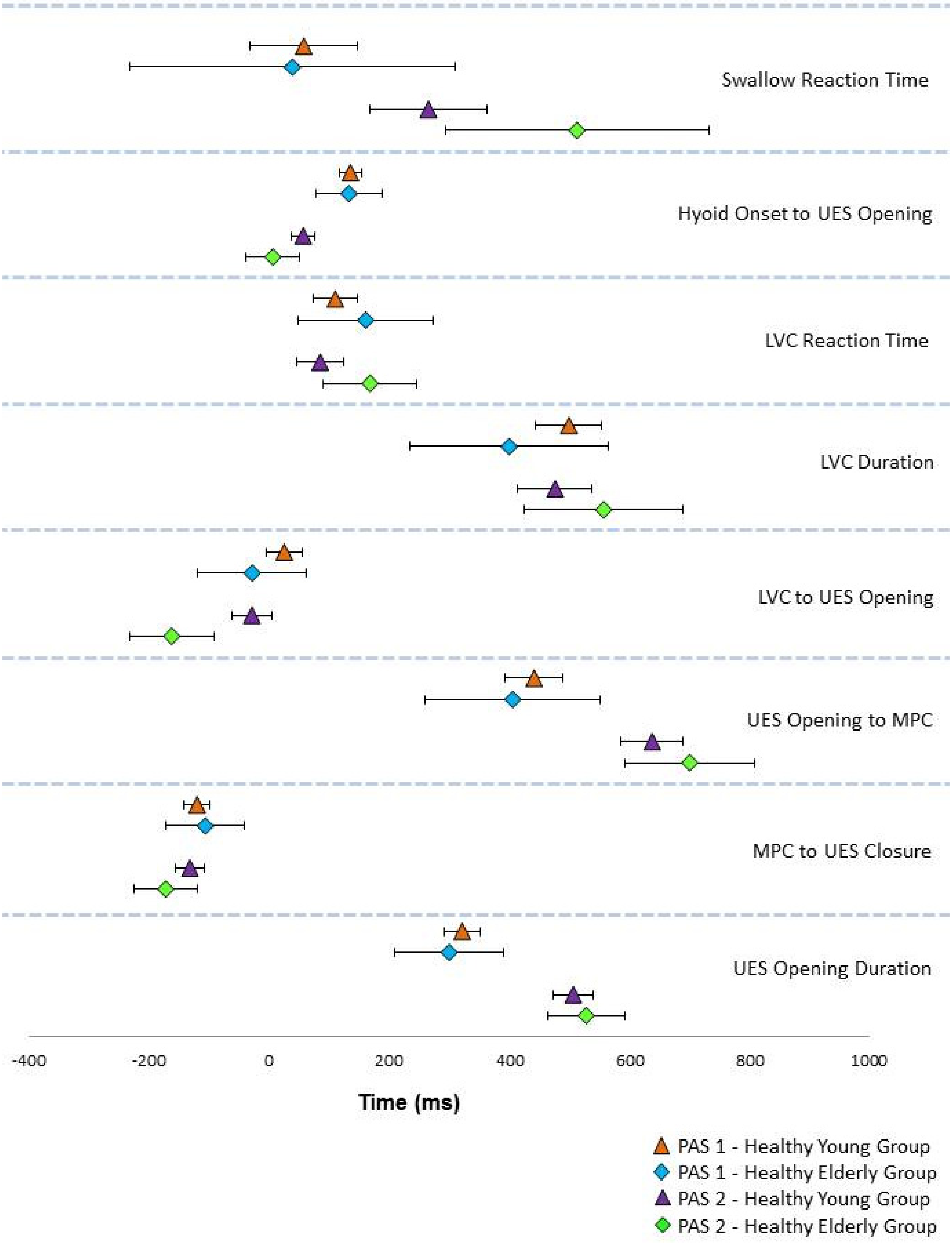
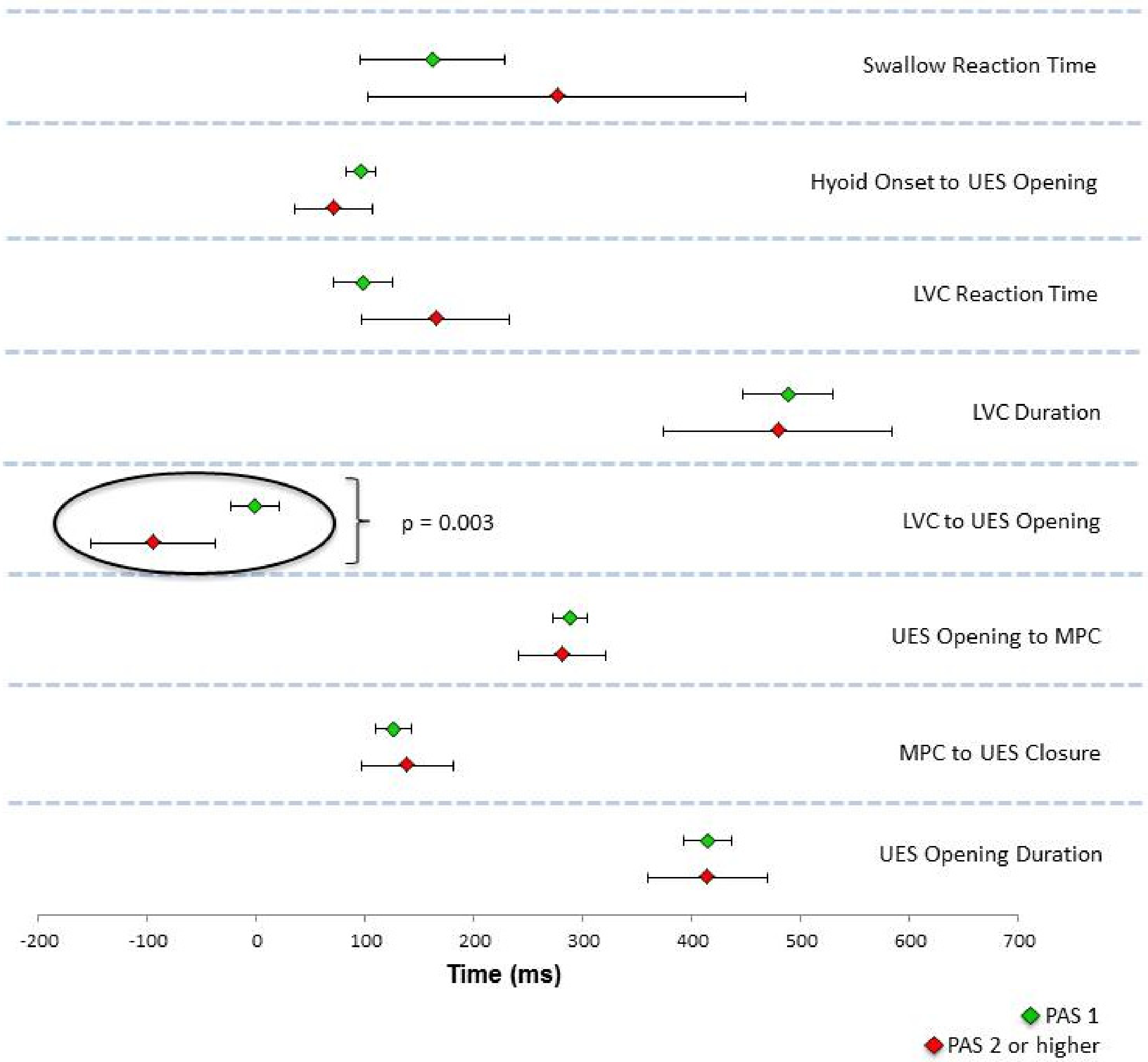


Figure 6 - The effect of PAS score (1 vs 2 or higher) on timing measures in the healthy young and healthy elderly groups.



6.5 Differences in timing measures related to Penetration-Aspiration Scale score in the healthy elderly group vs the elderly group at risk of dysphagia

The analysis of differences in timing measures between participants with PAS scores of 1 and those with transient penetration in the two older groups (healthy elderly and those at risk of dysphagia) identified a number of significant differences. Specifically, swallows with transient penetration were characterized by:

- a significantly shorter interval between hyoid onset and UESO;
- significantly longer LVCRT; and

- a significantly longer and more negative interval between LVC and UESO.

Additionally, a significant PAS score by sample interaction was found for laryngeal vestibule closure duration (p = 0.024). This interaction took the nature of shorter LVC durations on swallows involving transient penetration in the older adults at risk for dysphagia.

These results are shown in Table 5 and Figures 7 and 8.

Table 5 - Effect of PAS score on timing measures in the healthy elderly group and the elderly group at risk of dysphagia.

		Mean	SD	LCI	UCI	p-value
Swallow Reaction Time (ms)	PAS 1	350.91	340.27	178.05	523.77	0.090
	PAS 2 or higher	576.03	635.28	319.78	832.27	
Hyoid onset to UESO (ms)	PAS 1	96.49	64.85	78.80	114.19	0.015
	PAS 2 or higher	55.40	81.23	24.63	86.17	
LVCRT (ms)	PAS 1	123.63	105.50	94.76	152.49	0.000
	PAS 2 or higher	269.29	111.77	217.72	320.86	
Laryngeal Closure Duration (ms)	PAS 1	523.14	139.03	473.88	572.40	0.756
	PAS 2 or higher	508.33	162.82	420.61	596.06	
LVC to UES Opening (ms)	PAS 1	-28.90	104.52	-56.49	-1.30	0.000
	PAS 2 or higher	-210.42	76.62	-261.51	-159.33	
UES opening to MPC (ms)	PAS 1	415.78	82.89	385.89	445.66	0.357
	PAS 2 or higher	436.37	85.54	391.13	481.60	
MPC to UESC (ms)	PAS 1	104.13	63.38	83.59	124.70	0.406
	PAS 2 or higher	120.23	77.04	84,25	156.21	
UES opening duration (ms)	PAS 1	522.55	96.56	484.00	561.09	0.277
	PAS 2 or higher	550.36	79.98	495.67	605.04	

Figure 7 - Effect of PAS score on timing measures in the healthy elderly group vs the elderly group at risk of dysphagia.

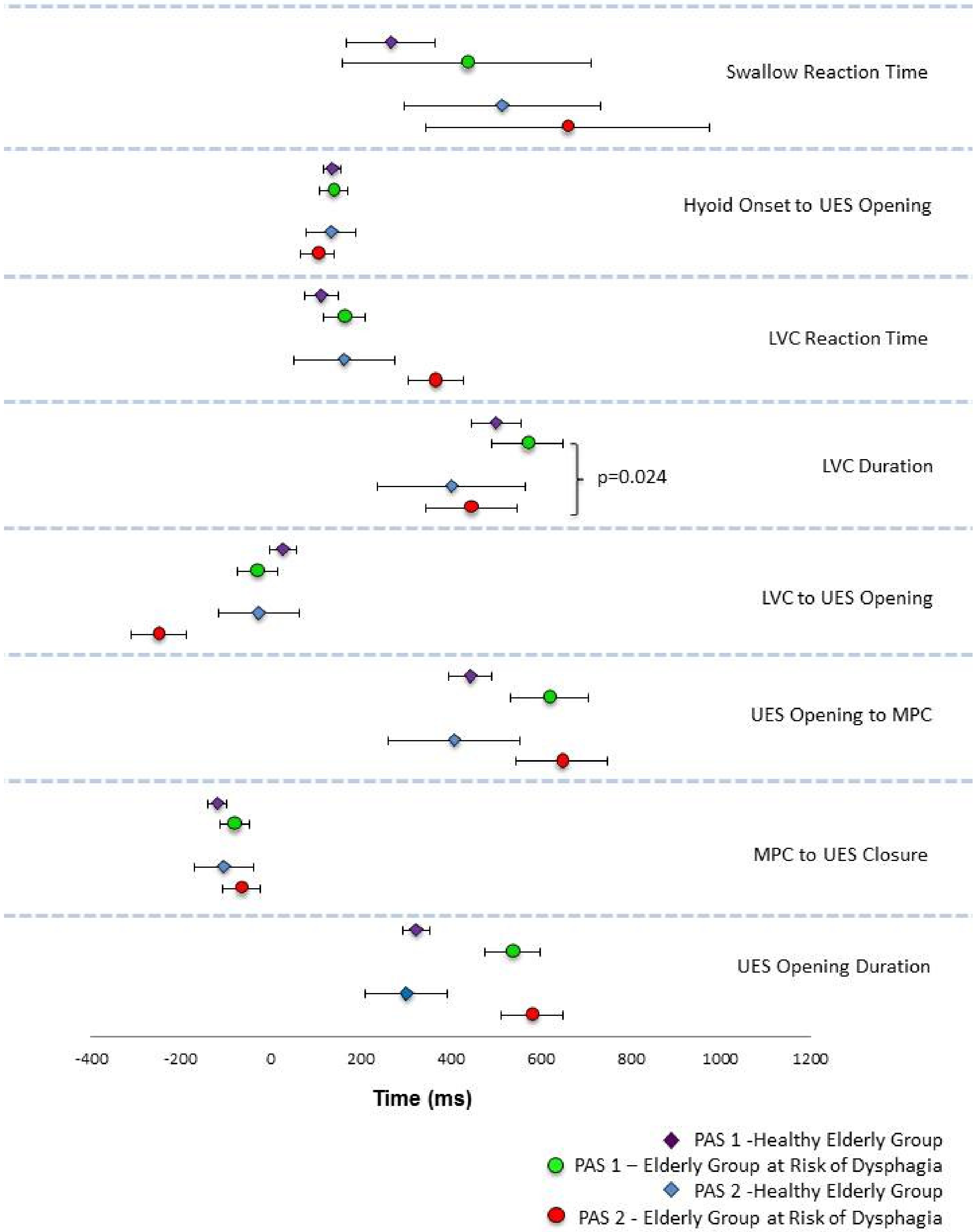
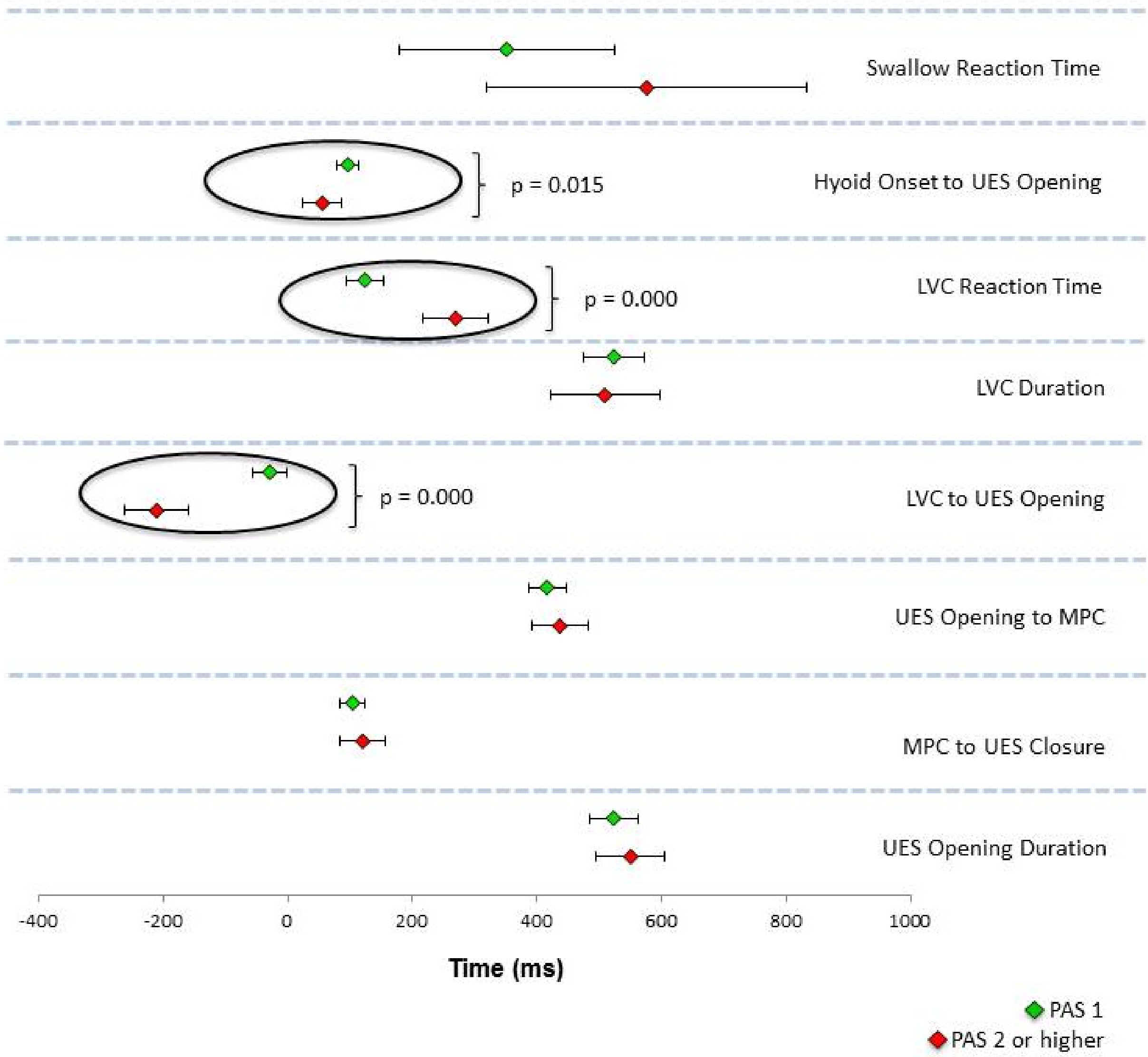


Figure 8 - The effect of PAS score (1 vs 2 or higher) on timing measures in the healthy elderly group vs the elderly group at risk for dysphagia.



Discussion

7. DISCUSSION

The results from this study show, in general, evidence to support the idea that temporal measures of swallowing are longer in healthy older adults in comparison with healthy young adults, and, even longer in older adults at risk for dysphagia. These data were in agreement with our hypotheses and with what is suggested in the literature in terms of longer transit times as characteristic of swallowing in the elderly [(1)(77)(78)(79)(80)].

7.1 Healthy young adults vs healthy older adults

The data in this study provide evidence that changes in timing measures are part of presbyphagia. In particular, the data suggest a pattern of longer reaction times or delayed responses in healthy older adults. This was seen in longer swallow reaction times (i.e. delayed onset of hyoid movement relative to bolus arrival in the pharynx), late laryngeal vestibule closure (i.e., after UES opening) and late maximum pharyngeal constriction relative to the time of UES opening. These findings are consistent with the conclusions of the recent systematic review by Namasivayam-MacDonald and colleagues[(44)].

Accordinly to Logemann et al (2013), another characteristic of aging is slowness of movement [(81)]. In this study, we did not specifically measure movement kinematics such as the velocity or duration of hyoid movement. We also did not specifically measure bolus transit times. Typical pharyngeal bolus transit time measures would be similar to the combination of the swallow reaction time and interval from hyoid onset to UES opening parameters in this study. We found longer swallow reaction times but shorter intervals from hyoid onset to UES opening in the healthy older participants in this study. Post-hoc analysis using the combination of these two parameters did show a significant effect of age ($p = 0.02$), with longer combined durations in the older participants (95% confidence interval: 250.71 to 443.84 ms) compared to the healthy younger controls (95% confidence interval: 103.53 to 279.91 ms).

However, our study also suggests that certain timing measures do not change with healthy aging. Importantly, two of these parameters (laryngeal vestibule closure reaction time and laryngeal closure duration) are directly involved in airway protection. Additionally, the interval between maximum pharyngeal constriction and upper esophageal sphincter closure remained unchanged. These findings suggest that it is reasonable to conclude that healthy elderly people generally retain the ability to perform safe and efficient swallowing despite the timing changes seen elsewhere in the analysis. One finding of potential concern in our study, is the fact that laryngeal vestibule closure occurred late, i.e. after upper esophageal sphincter opening in the healthy older group. This was opposite to the pattern seen in the healthy younger subjects and is in agreement with previous studies (5) (48) (49). Delayed LVC has been associated with risk of aspiration (5)(64)(85)(86).

Evidence of longer reaction times or apparent delays in the initiation of swallowing movements in healthy older adults is interesting. This suggests some sort of issue in the central pattern generator, either involving sensory deficits, or prolonged latencies to motor response (2)(87). Such evidence is not new. Kim & McCullough (2008) (88) found that stage transition duration was longer in their elderly research participants. Martin-Harris et al. (2007) (89) reported that with 5ml liquid boluses, in subjects aged >50 years old, hyoid movement began after the bolus had passed the mandible, and quite frequently after the bolus had reached the vallecular pit. This evidence sets up the possibility that interventions involving heightened sensory input might benefit older adults by facilitating a more timely swallow response.

In this study, timing measures involving UES function were also longer in the healthy older group in comparison with healthy young adults. Those included the upper esophageal sphincter opening duration and the interval from upper esophageal sphincter opening to maximum pharyngeal constriction. These results are consistent with previous literature and the results of the Namasivayam-MacDonald meta-analysis (44)(70) (90) and suggest that the bolus may be moving more slowly through the UES, requiring longer opening durations. There was evidence that reduced tongue strength in older adults may be one factor that could contributes to slower bolus movement (91).

One issue that is challenging when comparing swallow timing measures across the literature is the question of whether to measure events relative to a zero time point that is early in the swallowing sequence, such as the bolus passing an anatomical landmark (e.g. posterior nasal spine, faucial arches or ramus of mandible), or to reference events to a late event such as UES opening or closure

[74][92]. Further complicating this issue is the fact that some events are typically classified as bolus events, while others are classified as gestures and that the sequencing of these different types of events is not fixed [92][93][94]. In the approach used by Clave and colleagues [85], timing events are derived based on the opening and closing of four valves: the glossopalatal junction, the velopharyngeal junction, the laryngeal vestibule and the upper esophageal sphincter. However, the actions of these valves do not necessarily tell a story about the location of the bolus.

7.2 Healthy older adults vs older adults at risk for dysphagia

In this study, we extended our exploration of swallow timing beyond a population of healthy older volunteers to a sample of older adults referred for swallowing assessment and considered at risk for dysphagia. We specifically studies swallows from these individuals that were considered functional, meaning that there was no evidence of penetration-aspiration scale scores > 2 or of residue occupying more than 25% of the valleculae or pyriform sinuses. This specification allowed us to focus on changes in swallowing that distinguish healthy from at-risk seniors. Here, again, we found that differences in timing were present and took the general form of longer timing measures when risk of dysphagia was present. This finding supports the general assumption that the changes seen with advancing age represent a vulnerability and first step on the continuum towards dysphagia [28][85][95].

The interval from hyoid onset to UES opening measurement was significantly longer in the elderly group at risk of dysphagia. This finding was opposite to that observed in the comparison between healthy elderly and healthy young group and points to prolonged bolus transit times in those with dysphagia risk. The timing of laryngeal vestibule closure relative to hyoid onset (laryngeal vestibule reaction time) was also significantly delayed in the older adults at risk. This is suggestive of slower hyolaryngeal excursion, and was significantly associated with airway invasion in the form of transient penetration in the older adult analyses (see Table 5). Like the healthy older adults in our study, the older adults with dysphagia risk also displayed late laryngeal vestibule closure relative to upper esophageal sphincter opening. This delay was significantly longer in the elderly group at risk of dysphagia, and was significantly associated with transient penetration in all participant subgroups in this study (see Tables 4 and 5) Evidence of late LVC is consistent with previous studies

[5] [48] [49]. Our study points strongly to this phenomenon representing an important risk for aspiration, and a particularly important pathophysiological mechanism to target with intervention [5][64][85][86].

We did not find differences between the healthy older adults and older adults with dysphagia risk for the parameters of swallow reaction time, upper esophageal sphincter opening duration and laryngeal closure duration. However, all of these measures were longer in both older groups than in the healthy young adults.

7. 3 Differences in timing related to the occurrence of transient penetration

In all three of our participant groups there were examples of transient laryngeal penetration (i.e. PAS scores of 2). Daggett and colleagues (2016) [96] reported that older participants presented with more than twice the frequency of penetration than participants below age 50,and that this phenomenon was more common with liquid boluses [96][97]. Our results agree in part with this study, showing a higher prevalence of penetration in the elderly group at risk of dysphagia, in comparison with the other groups. Few differences in timing measures were found, but, as previously discussed, late laryngeal vestibule closure (either in the form of prolonged laryngeal vestibule closure reaction times or closure that occurred after UES opening) was strongly associated with these penetration events.Explanations for late LVC in the older participant groups in this study might include reduced sensory function, delayed transmission of sensory information to the swallowing central pattern generator or a delay in motor response in the central pattern generator. Previous literature has identified absent or diminished laryngeal sensory reflexes as a factor associated with airway invasion (penetration-aspiration) [57][63][98][99][100].

In this study, swallows with transient penetration were characterized by a shorter interval between hyoid onset and UES opening (reflecting later onset of hyoid movement), longer laryngeal vestibule closure reaction times and, a longer and more negative interval between LVC and UES opening. These findings point strongly to age-related sensory and functional changes representing a risk for impaired swallowing safety, and are consistent with previous literature [57][58][59][60][63][98][99][100].

In a previous study, by Steele and colleagues [101], in a large sample of 305 adults at risk for dysphagia, it was found that incomplete laryngeal vestibule closure increased the odds of a PAS score of 3 or higher almost 22 times, and increased the odds of a PAS score of 6 or higher by almost 8 times. They also found that LVC Reaction time was significantly longer for swallows with PAS scores of 3 and higher compared to PAS scores of 1 or 2.

It is important to understand the association between different timing parameters and penetration-aspiration in order to establish boundary values for these measures that can be validated to dissociate functional from impaired swallowing [(102)]. In our study, the timeliness of laryngeal vestibule closure differentiated swallows with penetration from swallows with no airway invasion. As with previous studies [(103)], once LVC was achieved, the duration of LVC did not differentiate between participants with or without airway invasion in our healthy participants. However, in the participants with dysphagia risk, significantly shorter LVC durations were associated with transient penetration. It should be noted that the previous studies have not focused on the specific comparison of PAS scores of 1 vs 2, but rather on aspiration (PAS scores of 6 and higher) compared to lower scores [(103)].

Conclusion

8. CONCLUSION

8.1 Temporal measures for the three groups:

We found longer swallow timing measures in healthy older adults in comparison with healthy young adults. In particular, the data suggest late hyoid onset (longer swallow reaction time and shorter time from hyoid onset to UES opening), late LVC (*after* UES opening), late MPC relative to UES opening, longer UES opening as features of presbyphagia.

Participants at risk for dysphagia displayed significantly longer timing intervals from Hyoid onset to UES opening, Laryngeal Vestibule Closure Reaction Time, and UES Opening to MPC. The interval from MPC to UES Closure was significantly shorter in those with dysphagia risk, suggesting late MPC. LVC to UES opening was negative in both groups, suggesting late LVC (after UES opening). Dysphagia risk in older adults is associated with longer swallow timing measures than those seen in similarly aged controls.

8.2 Effect of transient penetration of material into the laryngeal vestibule

In both of the healthy groups in this study, there was a tendency for longer laryngeal vestibule closure reaction time and late closure of the laryngeal vestibule relative to UES opening to be associated with transient penetration. For both older groups (healthy elderly and those at risk of dysphagia), transient penetration was associated with a shorter interval between hyoid onset and UESO, longer LVCRT and a longer and more negative interval between LVC and UESO. Also, shorter LVC durations were associated with transient penetration in the older adults at risk for dysphagia.

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Attachment

ATTACHMENT A

HOSPITAL DAS CLÍNICAS DA FACULDADE DE MEDICINA
DE RIBEIRÃO PRETO DA UNIVERSIDADE DE SÃO PAULO

HC FMRP-USP RIBEIRÃO PRETO

Ribeirão Preto, 10 de julho de 2014

Ofício nº 2363/2014
CEP/MGV

Prezados Senhores,

O trabalho intitulado **"EFEITO DO ENVELHECIMENTO NA BIODINÂMICA DA DEGLUTIÇÃO DE INDIVÍDUOS SAUDÁVEIS"** foi analisado pelo Comitê de Ética em Pesquisa, em sua 389ª Reunião Ordinária realizada em 07/07/2014 e enquadrado na categoria: **APROVADO,** bem como o **Termo de Consentimento Livre e Esclarecido,** de acordo com o Processo HCRP nº 8645/2014.

De acordo com Carta Circular nº 003/2011/CONEP/CNS, datada de 21/03/2011, o sujeito de pesquisa ou seu representante, quando for o caso, deverá rubricar todas as folhas do Termo de Consentimento Livre e Esclarecido – TCLE – apondo sua assinatura na última do referido Termo; o pesquisador responsável deverá da mesma forma, rubricar todas as folhas do Termo de Consentimento Livre e Esclarecido – TCLE – apondo sua assinatura na última página do referido Termo.

Este Comitê segue integralmente a Conferência Internacional de Harmonização de Boas Práticas Clínicas (IGH-GCP), bem como a Resolução nº 466/12 CNS/MS.

Lembramos que devem ser apresentados a este CEP, o Relatório Parcial e o Relatório Final da pesquisa.

Atenciosamente.

Marcia Villanova

DRª. MARCIA GUIMARÃES VILLANOVA
Coordenadora do Comitê de Ética em Pesquisa do HCRP e da FMRP-USP

Ilustríssimos Senhores
PROF.DR. ROBERTO OLIVEIRA DANTAS(Orientador)
WESLANIA VIVIANE DO NASCIMENTO
Depto. de Clínica Médica

Campus Universitário – Monte Alegre
14048-900 Ribeirão Preto SP

Comitê de Ética em Pesquisa HCRP e FMRP-USP
FWA-00002733;IRB-00002186 e Registro PB/CONEP n 5440
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ATTACHMENT B

Toronto General
Toronto Western
Princess Margaret
Toronto Rehab

University Health Network
Research Ethics Board
10th Floor, Room 1056
700 University Ave.
Toronto, Ontario, M5G 1Z5
Phone: (416) 581-7849

NOTIFICATION OF REB RENEWAL APPROVAL

Date: July 26, 2017

To: Catriona Steele
Room 12-101; Room 12-101, University Centre;
Toronto Rehabilitation Institute; 550 University
Avenue, M5G 2A2; Toronto, Ontario, Canada

Re: 16-5752
Revealing swallowing pathophysiology through the
ASPEKT method (Analysis of Swallowing Physiology:
Events, Kinematics and Timing): A knowledge
translation project

REB Review Type:	Delegated
REB Initial Approval Date:	August 4, 2016
REB Renewal Approval Effective Date:	August 4, 2017
Lapse In REB Approval:	N/A
REB Expiry Date:	August 4, 2018

The University Health Network Research Ethics Board has reviewed and approved the Renewal (16-5752.1) for the above mentioned study.

Best wishes on the successful completion of your project.

Sincerely,
Marina Mikhail
Ethics Coordinator, University Health Network Research Ethics Board

For: Ann Heesters
Co-Chair, University Health Network Research Ethics Board

The UHN Research Ethics Board operates in compliance with the Tri-Council Policy Statement; ICH Guideline for Good Clinical Practice E6(R1); Ontario Personal Health Information Protection Act (2004); Part C Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations and the Medical Devices Regulations of Health Canada.

ATTACHMENT C

University Health Network
Research Ethics Board
10th Floor, Room 1056
700 University Ave.
Toronto, Ontario, M5G 1Z5
Phone: (416) 581-7849

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ATTACHMENT D

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Estamos convidando o senhor(a) como voluntário(a) para participar da pesquisa “Efeito do envelhecimento na biodinâmica da deglutição de indivíduos saudáveis”, sob responsabilidade da pós graduanda Weslania Viviane do Nascimento e do Prof Dr Roberto Oliveira Dantas.

Nosso estudo irá observar se há mudanças no ato de engolir e de respirar enquanto come, em jovens e idosos. Para isso serão realizados dois exames de deglutição, a avaliação videofluoroscópica e exame da respiração. Registraremos também idade, altura, peso e o número de dentes, ou se usa dentadura. Responderá a um pequeno questionário para verificar se você possui queixas para se alimentar.

A videofluoroscopia é um exame radiográfico onde podemos filmá-lo enquanto comerá uma torrada e tomará água pura e engrossada, misturados em contraste de bário, para que possamos visualizar a imagem.

Para o exame da respiração passaremos duas faixas elásticas e 3 eletrodos na superfície do seu tórax, para observarmos o movimento do tórax durante a deglutição e os batimentos do seu coração, um catéter abaixo do seu nariz para observamos como você respira, um eletrodo no seu queixo para sabermos quando você engoliu e um oxímetro no dedo indicador para observamos a oxigenação do seu sangue durante o exame. Neste exame você comerá os mesmos alimentos, mas não será necessário acrescentar bário.

Não será necessário repetir os exames em outro momento.

Ambos os exames serão realizados no Hospital das Clínicas de Ribeirão Preto e não oferecerão riscos desnecessários à sua saúde, visto que no primeiro exame o tempo de exposição à radiação é mínimo (aproximadamente 25s) e será controlado pelos pesquisadores.

Caso constatado alguma alteração na deglutição durante as avaliações, o senhor será encaminhado pelo médico responsável, se considerar oportuno, ao serviço de fonoaudiologia do mesmo hospital, para intervenção.

Sua identidade não será revelada e os dados coletados serão avaliados e analisados para ensino e pesquisa. Informamos que você poderá desistir a qualquer momento, sua desistência não causará prejuízo ou despesas. Você não receberá pagamento ou gratificação pela sua participação.

Aceitando participar deste projeto você estará contribuindo para o avanço da ciência, possibilitando o conhecimento sobre como pessoas sem doenças e com diferentes idades engolem, e colaborando para que possamos planejar melhor nossos tratamentos.

Declaro que recebi todas as informações da pesquisa acima relatada e concordo, voluntariamente, em participar deste estudo.

____

(Assinatura do voluntário)

Nome:____ RG:___________________

Pesquisador(a) ____________________________________ Assinatura______________

Weslania Viviane do Nascimento – CRFa 17.493 - Departamento de Clínica Médica - Faculdade de Medicina de Ribeirão Preto – USP - Telefone: 11 9 8301 2557 e-mail: weslania.nascimento@usp.br
Roberto Oliveira Dantas – CRM 17.430 - Orientador e Docente do Departamento de Clínica Médica - Faculdade de Medicina de Ribeirão Preto – USP - Telefone: 16 3602 2457 e-mail: rodantas@fmrp.usp.br