Characterisation of Dysphagia in Diverse Clinical Populations using Pharyngeal High-Resolution Manometry with Impedance

By

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DECLARATION BY AUTHOR

I certify that this work does not incorporate without acknowledgement any material previously submitted for a degree or diploma in any university and that to the best of my knowledge and belief it does not contain any material previously published or written by another person except where due reference is made in the text. Professional editing was not used during preparation of this thesis.

Signed

Mistyka Schar

ACKNOWLEDGEMENTS

The work presented in this thesis is representative of the multi-disciplinary collaboration required for the provision of comprehensive dysphagia assessment. I would like to acknowledge the team of Scientists, Speech Pathologists, Gastroenterologists, ENTs, Sleep Physicians and Intensivists for being not only supportive of this endeavour but being progressive in pursuing research opportunities that have important clinical applicability.

First, I would like to thank my supervisor, Professor Taher Omari, who mentored me in the Pharyngeal High-Resolution Manometry with Impedance (P-HRM-I) technology. I would like to recognise his support with the interpretation of the altered biomechanical patterns seen in these studies and the broader understanding of swallowing physiology as well as statistical analysis of the data presented in this thesis. I admire his genuine integrity and tireless pursuit of investigation with P-HRM-I technology in this field. I would like to thank Associate Professor Eng Ooi who supported my initial interest in clinical research more than five years ago and encouraged me to enrol in the PhD program. During this time, I have been welcomed and encouraged to participate in the ENT clinical research meetings and to be active in the planning of future clinical research projects.

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PUBLICATIONS DURING CANDIDATURE

Peer-reviewed Journal Articles:

The following publications reflect the dissemination of some of the research conducted as part of this research programme. They describe the observed biomechanical swallowing outcomes in two homogenous cohort studies and one interventional study (Appendix 3).

1. **Schar, MS.** Omari, TI., Woods, CW., Doeltgen, S., Athanasiadis, T., Cock, C., Chai Coetzer, C-L., Eckert, D.J., & Ooi, E.H. Swallowing biomechanics pre-multi-level upper airway surgery for obstructive sleep apnea. *Journal of Clinical Sleep Medicine*, accepted for publication 17 December 2021. doi 10.5664/jcsm9824. Online ahead of print.

This paper relates to the data presented in Chapter 6. It outlines the biomechanical swallowing outcomes of unchanged velopharyngeal contractile pressures, and reduced meso- and hypo-pharyngeal pressures and reduced UOS relaxation pressure following surgery, which have not previously been detected by other swallowing assessment techniques.

2. **Schar, MS.**, Omari, TI., Woods, CW., Ferris, L., Doeltgen, S., Lushington, K., Kontos, A., Athanasiadis, T., Cock, C., Chai Coetzer, C-L., Eckert, D.J., & Ooi, E.H. (2021). Altered swallowing biomechanics in people with moderate-severe obstructive sleep apnea. *Journal of Clinical Sleep Medicine, 17* (9), 1793-1803.

This paper relates to the data in Chapter 4. The biomechanical swallowing outcomes reported in the OSA cohort include altered UOS function, with an associated elevation of bolus distension pressure at the hypopharynx and increased velopharyngeal contractile pressures. These novel findings provide an advanced understanding of the mechanisms that characterize altered swallowing in people with OSA.

3. **Schar, M.S,** Omari, T.I., Fraser, R.J., Bersten, A.D. & Bihari, S. (2020). Disordered swallowing associated with prolonged oral endotracheal intubation in critical illness. *Intensive Care Medicine*, *46* (1), 140-142.

This paper reports on the findings presented in Chapter 7 in a critically ill cohort following extubation or decannulation. The distinct biomechanical patterns identified of increased BPT and altered UOS function may reflect the effects of sedation and analgesia. Additionally, pharyngeal pressures remaining within the normative ranges challenges the proposed mechanism of neuromuscular pharyngeal weakness in this cohort.

4. **Schar, M.,** Woods, C., Omari, T., Footner, L., Marshall, N., Doeltgen, S., Cock, C., Thompson, A, Nguyen, T., Athanasiadis, T. & Ooi, E. Pharyngeal tongue base Augmentation for Dysphagia (PAD): A prospective case series in patients post Head and Neck Cancer (HNC) Treatment.

This manuscript has been submitted to *Head and Neck* in December 2021 and relates to the data presented in Chapter 9.

Throughout my PhD Candidature I have contributed to a number of publications that were not directly part of my thesis.

1. Omari, T., Rommel, N., Tack, J., Szczesniak, M., Wu., P., **Schar, M.,** Doeltgen, S. & Cock, C. Transient Hypopharyngeal Intrabolus Pressure: Clinically Relevant or Normal Variant? *Neurogastroenterology & Motility* (2021)-*available online ahead of print* doi: 10.1111/nmo.14276.

This paper describes an observed brief increased intra-bolus pressure qualitatively on the P-HRM-I pressure topography plot. This phenomena is hypothesised to represent a timing impairment of the coordination of bolus arrival in the hypopharynx and UOS relaxation.

2. Omari, TI., Ferris, L., **Schar, M.,** Cock, C. & Doeltgen, S. (2020). Multiple swallowing behaviour during high resolution pharyngeal manometry: Prevalence and sub-typing in healthy adults. Speech, Language and Hearing, DOI: 10.1080/2050571X.2020.1826109.

This paper describes P-HRM-I analysis in a healthy control cohort to define multiple swallowing behaviour. Further, it describes impedance derived analysis to sub-type multiple swallowing behaviour.

3. Ferris, L., Doeltgen, S., Cock, C., Rommel, N**., Schar., M.,** Carrión, S., Scholten, I. & Omari T. (2020). Modulation of pharyngeal swallowing by bolus volume and viscosity. *American Journal of Physiology-Gastrointestinal and Liver Physiology, 320* (1), G43-G53.

This paper provides normative range data of the core and additional P-HRM-I across young and aged cohorts. The most significant modulation of swallowing was demonstrated in hypopharyngeal intra-bolus pressure and UOS relaxation pressure and time. Sub-analysis of fluid volume and viscosity effects are described.

4. Omari, TI. & **Schar, M.** High-resolution manometry: What about the pharynx? (2018). *Current Opinion in Otolaryngology & Head and Neck Surgery, 26* (6), 382-391.

This paper reviews the P-HRM-I technology for pharyngeal swallowing assessment. It discusses the benefits of the technology in clinical care.

5. Huang, L., Athanasiadis, T., **Schar, M.,** Woods, C., Bassiouni, A., Martin, S., Bickford, J., Bihrari, S. & Ooi, EH. Bedside voice assessments cannot be used as a screening test for laryngeal injury following prolonged intubation in an intensive care population.

This manuscript has been submitted to *European Archives of Oto-Rhin-Laryngology* in November 2021.

PRESENTATIONS DURING CANDIDATURE

The following abstracts were accepted for presentation in oral or poster format and are inclusive of all of the homogenous cohort and intervention chapters presented in this thesis.

1. **Schar, M.**, Woods, C., Cock, C., Doeltgen, S., Ferris, L., Ooi, E., Athanasiadis, T. & Omari, T. Classification Framework for High-Resolution Pharyngeal Manometry (P-HRM-I) Interpretation of Pharyngeal Swallowing. Laryngology Society of Australasia (LSA) Virtual Conference. Oral presentation, November 2021. *(Chapter 10)*

2. **Schar, M.,** Woods, C.W., Ferris, L., Doeltgen, S., Chai-Coezter, C.-L., Athanasiadis, T., Cock, C., Omari, T.I. & Ooi, E. Swallow biomechanics in obstructive sleep apnoea syndrome. South Australian Allied Health Research Forum. Oral presentation, October, 2021. *(Chapter 4)*

3. **Schar, M.**, Omari, T., Woods, C., Cock, C., Doeltgen, S., Athanasiadis, T. & Ooi, E. Swallowing outcomes following multilevel upper airway surgery for obstructive sleep apnea. The Australian Society of Otolaryngology Head and Neck Surgery (ASOHNS) Virtual Conference, Melbourne. Oral presentation, September 2021. *(Chapter 6)*

4. **Schar, M.,** Omari, TI., Woods, CW., Doeltgen, S., Ferris, L., Cock, C., Athanasiadis, T. and Ooi, E.H. High-resolution pharyngeal manometry identifies specific biomechanical outcomes in patients with dysphagia following head and neck cancer treatment. Australian and New Zealand Head and Neck Cancer Society (ANZHNCS) Virtual Conference, Queenstown, New Zealand. Poster presentation, August 2021. *(Chapter 8)*

5. **Schar, M.,** Woods, C.W., Ferris, L., Doeltgen, S., Chai-Coezter, C.-L., Athanasiadis, T., Cock, C., Omari, T.I. & Ooi, E. Altered swallow biomechanics in moderate-severe obstructive sleep apnoea syndrome. European Society of Swallowing Disorders (ESSD) Online Virtual Congress, Spain. Oral presentation, October, 2020. *(Chapter 4)*

6. **Schar, M.**, Omari, T.I, Cock, C., Marshall, N., Woods, C., Athanasiadis, T. & Ooi, E. Pharyngeal augmentation for dysphagia (PAD): A novel surgical approach in dysphagia management post Head and Neck Cancer (HNC). Australian and New Zealand Head and Neck Cancer Society (ANZHNCS) Conference, Adelaide. Oral presentation, November 2019. *(Chapter 9)*

7. **Schar, M.,** Omari, T.I., Cock, C., Bersten, A. & Bihari, S. Association between disordered swallowing and endotracheal intubation in critically ill patients: A high resolution manometry study. Dysphagia Research Society (DRS) Conference, San Diego, USA. Oral Presentation, March 2019. *(Chapter 7)*

8. **Schar, M.,** Omari, T.I., Cock, C., Bersten, A. & Bihari, S. Predictors of Disordered Swallowing in Critically Ill Intensive Care Unit Patients. American Thoracic Society (ATS) Conference, Dallas, USA. Poster presentation, July 2019. *(Chapter 7)*

GRANTS AND AWARDS

During my candidature, I actively sought and obtained the following grants and scholarships to support the work conducted throughout the research programme.

1. Higher Degree Research Thesis Write-Up Stipend Scholarship. Flinders University Research Scholarship, 2021. ($14,000).

This scholarship supported my time to finalise writing of this thesis and complete manuscript submissions of thesis-related studies.

2. Pharyngeal Augmentation for Dysphagia (PAD) Therapy: A novel surgical approach in dysphagia management for HN Cancer survivors. College of Medicine and Public Health, Flinders University: Higher Degree Research Grant, 2019. ($4000; CI M.Schar).

This grant supported data collection and analysis with the results presented in Chapter 9.

3. Disordered swallowing associated with prolonged oral endotracheal intubation in critical illness. College of Medicine and Public Health Higher Degree Research Student Publication Award: Flinders University, 2019. ($500; M.Schar).

This award was received for the manuscript pertaining to Chapter 7.

4. Predictors for disordered swallowing in critically ill intensive care unit patients. American Thoracic Society (ATS), USA: The Hospital Research Foundation Travel Grant, 2019. ($3,500, M.Schar).

This award was received to support travel costs to present the data reported in Chapter 7.

5. Association of disordered swallowing with duration of oral endotracheal intubation in critically ill patients: A high-resolution manometry study. Dysphagia Research Society (DRS), USA: The New Investigator Award, 2019. ($1000, M.Schar).

This award was received for the oral presentation pertaining to the data presented in Chapter 7.

6. Characterisation of swallow dysfunction and neuronal degeneration in patients with obstructive sleep apnoea syndrome (OSAS). South Australia Health/University of South Australia Allied Health Research Collaboration Grant, 2018. ($35,000, CI M.Schar).

This grant was awarded to support the data collection and analysis for the data presented in Chapter 4.

7. Pharyngeal Augmentation for Dysphagia (PAD) Therapy: A novel surgical approach in dysphagia management for HN Cancer survivors. Australian and New Zealand Head and Neck Cancer Society, Research Foundation Board Grant, 2018. ($10,000, CI M.Schar).

This grant was awarded to support the data collection and analysis for the findings reported in Chapter 9.

LIST OF ABBREVIATIONS

AHI	apnoea hypopnoea index
AIM	automated impedance manometry
ANOVA	analysis of variance
ESS	Epworth Sleepiness Scale
FEES	fibreoptic endoscopic evaluation of swallowing
HCI	hypopharyngeal contractile integral
HNC	head and neck cancer
P-HRM	pharyngeal high-resolution manometry
P-HRM-I	pharyngal high-resolution manometry with impedance
IBP	hypopharyngeal intrabolus pressure
MCI	mesopharyngeal contractile integral
OSAS	obstructive sleep apnoea syndrome
PeakP	peak pressure
PhCI	pharyngeal contractile integral
PED	post-extubation dysphagia
PROM	patient-reported outcome measure
UPPP+/-CCT	uvulopalatopharyngoplasty with/or without coblation channelling of the tongue
SRI	swallow risk index
UES RT	upper oesophageal sphincter relaxation time
UEOS IRP	upper oesophageal sphincter integrated relaxation pressure
UESMax Ad	upper oesophageal sphincter maximum admittance
VCI	velopharyngeal contractile integral

VFSS	videofluoroscopic swallowing study
VM	videomanometry

Note to the reader

Throughout this thesis the Australian English spelling of upper oesophageal sphincter (UOS) is followed. However, the spelling and acronym of upper esophageal sphincter (UES) is used in relation to the P-HRM-I internationally derived metrics for consistency with the published outcomes.

PREFACE

The research presented in this doctoral thesis grew from my interest as a clinician with 10 years' experience as a speech pathologist working in dysphagia assessment and management, in the acute and sub-acute settings of ENT, Head and Neck Cancer and ICU. It was apparent to me the need for refined measures in oropharyngeal swallowing assessment to enable identification of the underlying pathophysiological mechanisms that contribute to the manifestations of dysphagia and to direct swallowing rehabilitation exercises. I have been provided with the remarkable opportunity to understand pharyngeal high-resolution manometry with impedance technology (P-HRM-I) under Professor Omari in the assessment of oropharyngeal dysphagia within the context of clinical cohorts of varying dysphagia severity with the clinical support of Associate Professor Ooi.

ABSTRACT

Oropharyngeal swallowing difficulty (dysphagia) is a symptom resulting from impairment or disorder affecting the swallowing mechanism. The reported prevalence of dysphagia varies but in some patient groups can reach as high as 50%. Dysphagia is an important health issue as it can negatively impact quality of life and is associated with malnutrition, dehydration and aspiration pneumonia, contributing to increased health care utilization and cost. Videofluorscopy swallowing study (VFSS) is considered the current gold-standard of swallow assessment, however this method has no universally accepted set of quantitative measures resulting in variability in interpretation and subsequent treatment planning. Pharyngeal high-resolution manometry with impedance (P-HRM-I) provides precise and quantative measures of pharyngeal and upper oesophageal sphincter (UOS) pressures integrated with bolus transit. Unlike other swallowing assessment methods, P-HRM-I can identify and localise alterations in the swallowing mechanism and determine the underlying pathophysiological breakdown leading to dysphagia. This thesis endeavours to expand our understanding of the biomechanical swallowing patterns across a range of homogenous cohorts and following interventional procedures, providing novel findings that characterise dysphagia in these cohorts.

The following P-HRM-I swallowing assessments were conducted in four homogenous cohorts: obstructive sleep apnoea (OSA; n=19), post- modified uvulopalatopharyngoplasty with/without coblation channelling of the tongue (mUPPP+/-CCT) surgery for OSA (n=21), critically ill post-extubation and/or decannulation (n=19), and post-Head and Neck Cancer treatment (HNC; n=14); and as an interventional outcome measure in two cohorts: pre- and post- mUPPP+CCT surgery for OSA (n=10) and pre- and post-tongue base augmentation following HNC treatment (n=6). P-HRM-I Core and Additional measures were reported consistent with international recommendations.

Novel and distinct biomechanical swallowing patterns were identified in the cohort studies, including: (1) altered UOS function with increased velopharyngeal contractile pressures in the OSA and post-mUPPP+/-CCT cohorts, (2) altered UOS function and increased bolus presence time in the critically ill following extubation and/or decannulation cohort, and (3) reduced pharyngeal contractile pressures with or without UOS dysfunction in the post-HNC treatment cohort; and in the interventional studies: (4) unchanged velopharyngeal contractile pressures, reduced meso- and hypo-pharyngeal pressures, and reduced UOS relaxation pressures post-mUPPP+CCT surgery for OSA, and (5) no significant biomechanical changes following tongue

base augmentation. However, subtle changes of improved UOS opening and relaxation were observed and hypothesised to indicate more efficient pharyngeal bolus transit.

The utilisation of P-HRM-I for swallowing assessment in the research setting has increased in recent years, albeit with inconsistencies in reported outcome measures and variable evaluation of findings with dysphagia literature, yet the expansion of P-HRM in the clinical setting has been idling in the face of existing barriers. The novel findings in this thesis are important for the provision of meaningful translation of P-HRM-I technology to the clinical setting. In each of the studies, the application of P-HRM-I to determine the underlying pathophysiology and localise the mechanistic alteration in swallowing demonstrates the utility of P-HRM for clinical dysphagia assessment, with findings that can assist clinicians to provide better tailored and efficacious dysphagia management. The P-HRM-I derived biomechanical patterns identified in these studies have formed the foundation for proposing a P-HRM-I Classification Framework to assist clinicians in the interpretation of P-HRM-I assessment findings, which aims to address one of the barriers limiting the uptake of P-HRM-I in the clinical setting.

THESIS SYNOPSIS AND OUTLINE

The overall aim of this research program is to enhance the understanding of the swallowing biomechanics in different clinical dysphagia cohorts, using P-HRM-I measures. Unlike other swallowing assessment methods, P-HRM-I can identify and localise alterations in the swallowing mechanism to determine the underlying pathophysiological breakdown leading to dysphagia. This insight provides considerable opportunities for clinical translation of P-HRM-I into routine practice. Accordingly, the specific aims of this research program were to:

1. Determine the P-HRM-I measures and biomechanical patterns that characterise dysphagia in four distinct homogenous adult cohorts with differing medical aetiologies, when compared to healthy controls.
2. Explore the utility of P-HRM-I as an interventional outcome measure in two different adult cohorts and identify biomechanical changes following the intervention to determine its mechanistic effect on swallow function.

This thesis is presented in 11 chapters (Figure I). In **Chapter 1**, a review of the current literature is presented that examines (1) the current understanding of the normal physiology swallowing with the underpinning anatomy and neurology, (2) the epidemiology of dysphagia with a focus on the four homogenous cohorts, (3) the swallowing assessment methods commonly utilised in clinical practice, and (4) the utility of P-HRM with/without impedance in swallowing assessment. This review has three aims: First, to provide an understanding of the biomechanical processes involved in normal pharyngeal swallowing and their complex interplay with underlying multi-dimensional neural mechanisms. This provides a background for processes and mechanisms that are discussed in more specific depth within the thesis chapters. Second, to provide an introduction and overview of the epidemiology of dysphagia centring on the homogenous cohorts investigated in this thesis. Finally, to provide an overview and evidence review of the various swallowing assessment methods, including patient-reported assessment, clinical assessment and visual instrumental assessments, with more specific focus on P-HRM with and without impedance in pharyngeal dysphagia assessment. **Chapter 2** presents the thesis aims, and **Chapter 3** describes the overall methodology utilised to explore swallowing biomechanics in the four homogenous cohorts and two interventional studies.

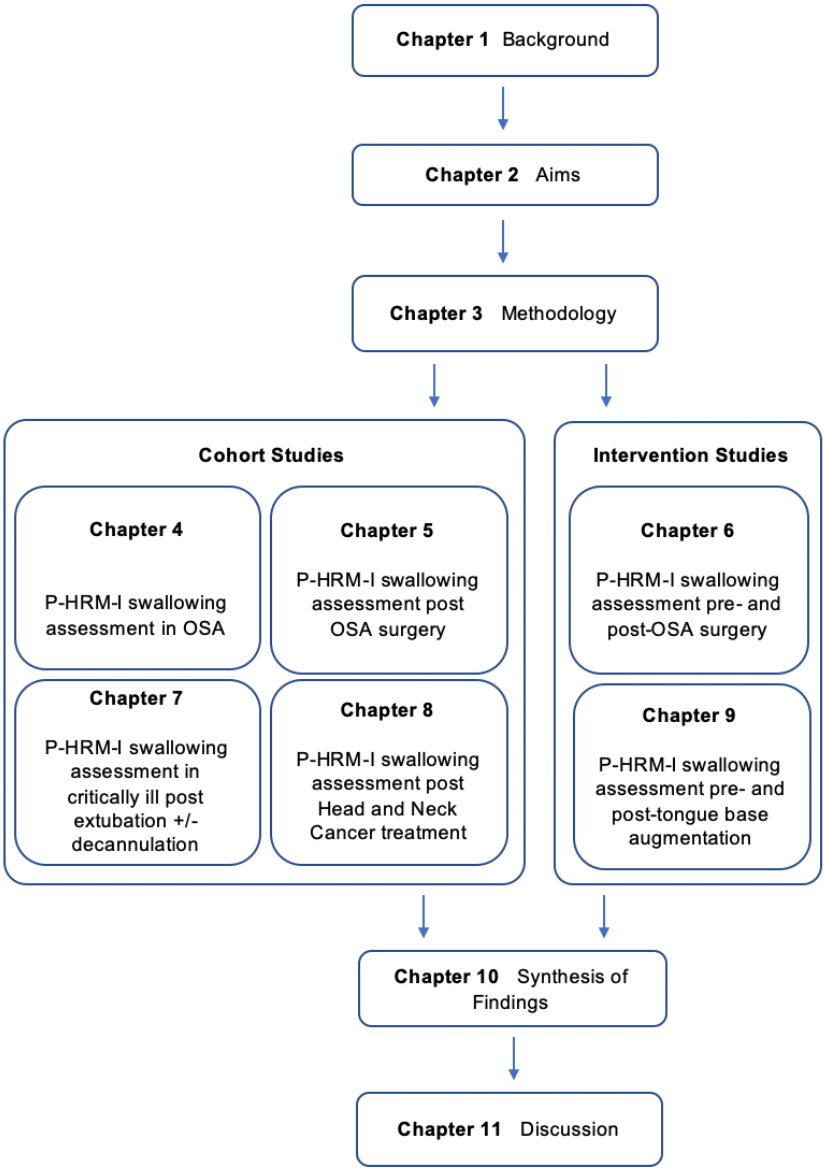

FIGURE I: THESIS OUTLINE

In **Chapter 4,** swallowing is evaluated in an OSA cohort using P-HRM-I. Dysphagia in people with OSA is currently gaining considerable attention, however the impaired swallowing mechanisms that contribute to dysphagia are unclear. P-HRM-I identified distinct biomechanical patterns in the OSA cohort compared to healthy controls, including altered UOS function, with an associated elevation of bolus distension pressure at the hypopharynx and increased velopharyngeal contractile pressures. These findings could indicate a neuroregulatory impairment of UOS function, presenting as a swallowing motor response that is less effective in

accommodating for changes in bolus volume and consistency. Additionally, the elevated velopharyngeal contractile pressures are hypothesised to represent a compensatory mechanism to overcome the UOS dysfunction. These novel biomechanical findings provide a more advanced understanding of the mechanisms that characterize altered swallowing function in people with OSA.

Surgical techniques are currently utilised as a management option for OSA, however dysphagia has historically been reported post-surgery. The literature has predominantly reported on historical surgical techniques using VFSS assessment to assess swallowing outcomes. As a result, swallowing biomechanics following a contemporary surgical technique for OSA, such as mUPPP+/-CCT, have not been investigated. In **Chapter 5,** swallowing biomechanics were assessed post-mUPPP+/-CCT surgery and compared to healthy controls. This study was an extension of a previous study from our group, published in 2018 (1) with a small cohort (n=12), which has now been expanded (n=21) providing a larger data set for analysis. When compared with healthy controls, the P-HRM-I outcomes in the post-mUPPP+/-CCT surgery cohort revealed velopharyngeal contractile pressures that were elevated post surgery, which differs from historical reports of velopharyngeal insufficiency following historical surgical techniques. Additionally, elevated UOS relaxation pressures and intra-bolus pressures are indicative of UOS restriction during swallowing. The findings presented in this Chapter confirm our groups' original findings(1), of UOS restriction during swallowing in participants post-OSA surgery. However, when these altered swallowing outcomes are considered together with those reported in the OSA cohort pre-surgery (in Chapter 4), the results are suggestive of biomechanical patterns associated with pre-existing OSA, rather than a swallowing impairment resulting from the mUPPP+/-CCT surgery.

While the findings from Chapter 5 provide novel insights, a limitation of the study was that it did not compare post-surgical swallowing outcomes to pre-surgical baseline in the same cohort. The prospective evaluation of swallowing function pre- and post-upper airway surgical intervention for the management of OSA has not previously been conducted in relation to the mUPPP+CCT surgical technique. In **Chapter 6**, P-HRM-I was utilised as an interventional outcome measure to compare the swallowing biomechanics post-mUPPP+CCT surgery to pre-surgical baseline in a moderate-severe OSA cohort. This study identified the following key biomechanical outcomes following surgery: (1) velopharyngeal contractile pressures were unchanged, (2) meso- and hypo-pharyngeal contraction pressures were reduced, and (3) UOS relaxation pressures were reduced. These biomechanical findings provide a new and quantified

evaluation of the effect of mUPPP+CCT surgery on swallowing function. Importantly, the results further supported the findings from Chapter 5 and Chapter 4, demonstrating increased contractile pressures in the velopharynx pre-surgery that remained elevated following surgery, indicating that the mUPPP+CCT surgical technique does not change these pressures. These are important findings that have clinical relevance for health professionals involved in the management of people with OSA.

In the Intensive Care Unit, dysphagia is a concerning symptom that is frequently reported following extubation and/or decannulation. Aspiration is the most frequently reported outcome measure, however the mechanisms that result in aspiration or altered swallowing function at the time of extubation and/or decannulation are seldom studied. In **Chapter 7**, P-HRM-I was utilised to assess swallowing biomechanics in the critically ill following extubation and/or decannulation and compare these to healthy controls. Distinct biomechanical patterns were identified in this cohort, including increased Bolus Presence Time (BPT) and altered UOS function, which may reflect the effects of sedation and analgesia. An unexpected biomechanical finding was the total pharyngeal pressures did not show a significant reduction in the critically ill following extubation and/or decannulation. This finding challenged one of the proposed mechanisms of dysphagia in this population, namely neuromuscular pharyngeal weakness due to disuse of the oropharyngeal musculature. This novel finding highlights the utility of P-HRM-I to reveal mechanisms that may, but also may not, contribute to dysphagia in this cohort.

Dysphagia is a well-documented outcome associated with HNC treatment. While various contributory mechanisms have been described, these have largely been observations from VFSS assessment. In **Chapter 8**, P-HRM-I was used to assess participants with moderate to severe dysphagia with a high prevalence of aspiration. The underlying biomechanical measures were determined and compared with healthy controls as well as correlated with visual instrumental assessment. Two distinct altered biomechanical patterns were identified in this cohort: (1) UOS dysfunction and (2) reduced pharyngeal contractility. Of these two patterns, only UOS dysfunction was correlated with pharyngeal residue and aspiration on VFSS. This is the first study where pharyngeal residue has been associated with UOS dysfunction in a post-HNC treatment cohort. Although reduced pharyngeal contractile pressures were also identified using P-HRM-I, these were not correlated with pharyngeal residue, differing to previous literature. This significant finding reflects the inherent limitations of VFSS to assess pharyngeal pressures and analyse UOS function and underscores the utility and importance of P-HRM-I in this setting.

A novel procedure that is gaining recognition for dysphagia management following HNC treatment is tongue base augmentation, which aims to target reduced tongue base volume believed to contribute to dysphagia. Functional swallowing outcomes following tongue base augmentation using adipose tissue (fat) have been reported, however evaluation of the swallowing biomechanics have not been studied. In **Chapter 9**, P-HRM-I was utilised as an interventional outcome measure to determine the effect of tongue base augmentation using hyaluronic acid on swallowing function compared to pre-surgical baseline. The results indicated improvements in UOS opening and relaxation following the novel procedure compared to baseline, which are suggestive of a subtle improvement of a more efficient transit of the bolus through the UOS. Along with biomechanical analysis of pharyngeal contractile pressures, VFSS-derived outcomes were also assessed which showed no change in aspiration and residue following the procedure compared to baseline. This is likely attributable to the conservative volumes of hyaluronic acid that were injected in our study that limited the effect of tongue base augmentation on functional swallowing outcomes.

Chapter 10 presents a synthesis of the individual P-HRM-I findings from the studies conducted throughout this thesis. Each of the P-HRM-I metrics are defined and discussed in relation to their contribution to the identification of abnormal swallowing features in each of the four observational study cohorts and the two interventional study cohorts, through which unique biomechanical pathophysiological swallowing patterns became apparent. Based on these identified swallow biomechanical patterns, the rationale and development of a P-HRM-I Classification Framework is then proposed. Although this Classification Framework is preliminary and requires further validation, it has been developed to bridge an implementation barrier regarding interpretation of P-HRM-I swallow assessments for clinicians. Ultimately, this will support translation of this technology into clinical practice.

Chapter 11 presents a general discussion that is drawn from the studies performed during the candidacy by interpreting the findings relative to each cohort in the context of the available literature. This includes an evaluation of the utility of P-HRM-I in the assessment of pharyngeal dysphagia, which is crucial given the potential of this technology to enhance the evaluation of swallowing by VFSS and FEES assessments. With this perspective, future directions of the application of P-HRM-I technology are discussed.

INTRODUCTION

Normal swallowing is a pressure-driven sequential process that occurs approximately 600 times per day and enables adequate bolus transit of saliva, food and drink to the stomach (2-5). Changes may occur at any of the biomechanical stages of swallowing, including oral, pharyngeal or oesophageal, resulting in ineffective bolus passage. Dysphagia (disordered swallowing) is a commonly reported symptom associated with a number of different underlying health conditions, which have a considerable impact on the individual and the broader community. Dysphagia has a reported prevalence of 16-20% in the general population but increases to as high as 50% in some specific groups (6, 7). It is associated with a range of comorbidities, including malnutrition, dehydration and aspiration pneumonia. These can lead to adverse health outcomes, affect quality of life, as well as contribute to increased health care services utilisation and hospital length of stay (7, 8).

Currently, the gold standard for the assessment of oropharyngeal dysphagia is the videofluoroscopy swallowing study (VFSS), a radiological procedure where bolus movement is observed in connection with oropharyngeal structural reconfiguration (9). However, without globally accepted quantitative metrics, the clinical reporting of VFSS is predominantly subjective and dependent on the experience of the observing clinician (10). The limitations of radiographically-derived observations for the assessment of swallowing to measure the dynamic muscle changes prior to bolus passage and the generated pressures during bolus movement were recognised in one of the earliest publications regarding manometric evaluation of swallowing more than 70 years ago (11). Since that time, the technological advancements of manometry have led to the development of high-resolution manometry (HRM), which has considerably more pressure sensors along the catheter, typically with 1 cm spacing, to provide detailed analysis of muscle contraction and relaxation during swallowing (12-15). HRM with impedance (HRM-I) is currently considered the gold standard in oesophageal motility assessment (16-18) with the application of this technology for the assessment of pharyngeal swallowing increasing over the past ten years (19-23).

This trans-nasal catheter-based assessment objectively quantifies swallowing function through combined analysis of the pressures generated from muscle contraction and/or relaxation and bolus movement that is captured using mucosal impedance measurement (16, 17). The clinical

application of HRM technology for pharyngeal swallowing assessment is now recognised as an emerging area of practice for speech pathologists in the United States of America (24) and Europe (22) and termed pharyngeal high-resolution manometry (P-HRM). However, in Australia the P-HRM technology has been research-related and not incorporated into routine clinical assessment (25), with uptake of this limited to a few research groups within teaching hospitals by the speech pathology profession. P-HRM has been used in pharyngeal swallowing assessment both without (26-28)(P-HRM) and with impedance (29, 30) (P-HRM-I) data.

The information generated by P-HRM-I has the potential to address some acknowledged deficiencies of VFSS, enabling a comprehensive swallowing assessment (31). Only a small number of centres regularly use P-HRM-I in clinical practice, with barriers to widespread uptake including limited training opportunities as well as ambiguous clinical indicators for suitable use, such as which patient cohorts would most likely benefit (32). In recent years, there has been an increasing number of publications reporting the normative data of pharyngeal swallowing using P-HRM-I in healthy cohorts and in both heterogenous and homogenous cohorts of patients with dysphagia (21). However, considerable variability in data acquisition and analysis, as well as the reporting of P-HRM-I measures (21) contributes to difficulty understanding the technology in the field of dysphagia. Additionally, as dysphagia is a symptom of various underlying medical conditions and diseases, ongoing investigation into the application of P-HRM-I measures is required. An increased clinical uptake of P-HRM-I assessment in pharyngeal dysphagia necessitates further establishment of these measures in a broad range of clinical populations.

The research presented in this thesis discusses and further establishes the contributions and utility of P-HRM-I measures for the assessment of pharyngeal dysphagia associated with a number of different aetiologies. It has attempted to expand the understanding of the biomechanical swallowing patterns across four differing homogenous cohorts. Please note that in this thesis, *homogenous* cohorts refer to participant populations according to their medical condition/disease. Additionally, longitudinal evaluation of biomechanical measures can quantify treatment effects on swallowing, as such two interventional studies examine the role of P-HRM-I as an outcome measure. The acquisition of new knowledge regarding pharyngeal mechanisms characterising altered swallowing function in various cohorts and longitudinally following interventions continues the progression to an evidence-base for P-HRM-I, which is critical for its future recognition and translation to the clinical setting.

1. BACKGROUND

1.1 Anatomy and Physiology of Swallowing

Swallowing is a dynamic sensorimotor event that provides two interdependent movements: (1) propels food and fluids from the oral cavity through the pharynx and oesophagus to the stomach, and (2) protects the upper respiratory tract by temporary laryngeal occlusion preventing aspiration (33-35). Swallowing requires the sequential coordination of both voluntary and reflexive contraction and relaxation of 26 pairs of muscles through the oral, pharyngeal and oesophagus (36). These muscles are innervated by six cranial nerves (CN): the trigeminal (CN V), facial (CN VII), glossopharyngeal (CN IX), vagus (CN X), accessory (CN XI), and hypoglossal (CN XII) nerves (37), described in further detail in 1.2 Neural Control of Swallowing. The swallowing sequence occurs over a short duration of time, with the oropharyngeal phase of swallowing ranging between 0.6-1 second (34) and the oesophageal phase ranging between 8-20 seconds (38, 39).

Contemporary knowledge of swallowing physiology has been derived from human and animal research using fluoroscopic, endoscopic, manometric and electromyographic (EMG) studies (40-42). The swallowing process is a continuous sequence of events that is commonly divided into distinct phases according to the location of the bolus (43, 44). The difficulty in delineating the phases is well recognised due to the interplay between them, however they are beneficial for descriptive purposes (41). The physiology of swallowing with the underpinning anatomy and neurology are described within the four-phases model: the oral preparatory, oral transport, pharyngeal and oesophageal phases (45), illustrated in Figure 1.1.

Figure 1-1THE FOUR STAGES OF SWALLOWING.
1 = Oral Preparatory, 2 = Oral Transport, 3-5 = Pharyngeal and 6 = Oesophageal (46).

1.1.1 Oral Preparatory Phase

Prior to the commencement of eating and drinking at the oral phase, perception of olfaction (smell) and visual stimuli prompt anticipation of ingestion and stimulate salivation, which is necessary for bolus preparation and transport (47, 48). The oral preparatory phase then ensues, which involves structures and processes within the oral cavity.

The oral cavity, also known as buccal cavity, is a chamber extending from the lips anteriorly, to the oropharyngeal isthmus posteriorly, at the palatoglossal arch (Figure 1.2). It consists of: (1) the vestibule, the space between the lips/cheeks and the teeth and includes the anterior and lateral sulci, and (2) the oral cavity proper, the space formed by the roof of the mouth (dental arches (alveolar bone) of the maxilla and soft palate), and the floor of the mouth (dental arches (alveolar bone) of the mandible and tongue) (36, 49). The palatoglossal arch, known as the anterior faucial pillar, consists of folds of tissue surrounding the palatoglossal muscle (49) and marks the border between the oral cavity and the pharynx, which begins at the palatopharyngeal arch (44, 50).

Figure 1-2 FRONTAL VIEW OF THE ORAL CAVITY (36)

In the oral cavity, the oral preparatory phase involves mastication of solid food mixed with saliva to form a cohesive bolus (50, 51). The duration of this phase is highly variable depending on the food texture, liquid consistency, taste, environment, dentition, hunger and motivation (52-54). This phase is initiated with the opening of the mouth and jaw to accept entry of the food/fluid, which occurs through the inhibition of the orbicularis oris muscle (innervated by CN VII, facial nerve), and depression and protraction of the mandible via the lateral pterygoid, digastric, and mylohyoid muscles (Figure 1.3) (55, 56). The food/liquid enters the oral cavity where the tongue forms a midline groove to receive the bolus (57). Movement of the tongue is then responsible for bolus movement within the oral cavity, which occurs through a complex and dynamic three-dimensional arrangement of the intrinsic tongue muscles (including the superior and inferior longitudinal, vertical and transverse muscle fibres) and extrinsic tongue muscles (hyoglossus, styloglossus, genioglossus and palatoglossus) (56, 58). The extrinsic tongue muscles are shown in Figure 1.3 below.

Figure 1-3 LATERA OF THE FACIAL, EXTRINSIC TONGUE AND PHARYNGEAL MUSCLES (59)

The anterior two-thirds of the tongue also relays sensory information (including taste, touch, pain, and temperature) via the lingual branch of the trigeminal nerve (CN V) (60). With the bolus held by the tongue, the lips close, largely through the contraction of the orbicularis oris muscle

(CN VII) (56). The jaw also closes, through elevation of the mandible via activation of the temporalis, masseter and medial pterygoid muscles (innervated by V3 mandibular branch of CN V, trigeminal nerve), which assists in oral containment of the food/liquid.

For liquids, the bolus is held in the mouth between the anterior surface of the tongue and the dental arch of the hard palate or on the floor of the mouth (36). To prevent leaking of the liquid bolus into the oropharynx before the swallow, the soft palate muscles depress via contraction of the palatoglossus muscles (innervated by the pharyngeal plexus from CN X, vagus nerve) and elevate the back of the tongue to create a posterior glossopalatal seal (36, 61, 62), as demonstrated in Figure 1.4. During the swallowing process of solid food 'stage 1 transport', the food is positioned on the tongue and moved posteriorly on the occlusal surface of the molars by the tongue (36, 56). The buccinator muscle (innervated by CN VII) maintains the bolus positioning against the teeth (Figure 1.3. Mastication ensues, which reduces food particle size and prepares the bolus for swallowing. There are four predominant muscles of mastication, three of which contribute to closing of the jaw (temporalis, masseter, and medial pterygoid) and one to jaw opening (lateral pterygoid). The trigeminal nerve (mandibular branch, CN V) that innervates these muscles also transmits sensory information via the mandibular and maxillary branches, which enables modification of mastication as required. Sensory feedback receptors of the periodontal region and temporomandibular joint also function to modify movements via reflexive feedback processes, to continuously adapt throughout mastication (63, 64). These cyclic jaw movements are temporo-spatially coordinated with the cyclic movements of the tongue, cheek and soft palate (65, 66).

Figure 1-4 ORAL PHASE OF SWALLOWING.

(A) Bolus positioned in the mouth between the anterior surface of the tongue and the hard palate. The black arrows highlight the posterior seal of the soft palate and tongue to prevent liquid spilling to the oropharynx.

(B) The anterior two-thirds of the tongue elevates to produce peristaltic contact against the hard palate as seen making a 'v' shape with the indicated grey arrow (45).

Saliva contributes to bolus formation and preparation by altering the properties of the food through lubrication and secretion of the enzyme amylase until the food texture is suitable for swallowing (36). Saliva is produced by three paired glands: the parotid (stimulated via parasympathetic fibres of CN IX, glossopharyngeal nerve), and the submandibular and

sublingual glands (stimulated via parasympathetic fibres of CN VII, facial nerve), which accounts for 90% of saliva production (67). Saliva also has important functions in gustation (taste) (65, 68), as a solvent, and facilitates the delivery of tastants (molecules sensed by taste) to taste receptors. The taste receptors are largely concentrated in fungiform papillae on the tongue and the circumvallate papillae in the sulcus terminalis (67). Taste information is transmitted via the lingual branch of CN VII (facial nerve) from the anterior two-thirds of the tongue, CN IX (glossopharyngeal nerve) from the posterior tongue and from the pharyngeal aspect via CN X (vagus nerve) (67). Furthermore, retronasal olfaction contributes to the perception of flavour. This occurs during mastication when air is shunted up through the nasal cavity and odour molecules emerging from the oral cavity stimulate olfactory receptors (53).

1.1.2 Oral Transport Phase

The oral transport phase begins when the bolus is propelled posteriorly through the oral cavity (50, 51). Although there is a recognised sequence of tongue movements during the oral phase, these are not uniform and have been shown to vary widely (58, 69). During ‘stage II transport’, the food bolus aggregates on the dorsal surface of the tongue and is transferred to the oropharynx in repetitive transport cycles during jaw opening (70). The jaw and tongue are stabilised by the contraction of the muscles of mastication (submental muscles) (mylohyoid and anterior digastric muscles (innervated by CN V, trigeminal nerve), and geniohyoid muscles (innervated by CN XII, hypoglossal nerve and C1-C2)), and the remaining suprahyoid muscles (posterior digastric and stylohyoid muscles (innervated by CN VII, facial nerve)) (71). During mastication, the chewed food aggregates in the valleculae of the pharynx prior to swallowing, which normally takes between less than one second to approximately 10 seconds (72, 73). Once a portion of the masticated food or liquid is suitable for swallowing there is increased tongue muscle contraction, which pushes against the palate with movements directed posteriorly (Figure 1.4 B) (43, 64, 74). This results in increased intra-oral pressure generation immediately behind the bolus, with higher levels of pressure at the approximation of the mid palate and posterior tongue (58), which is responsible for bolus transport to the pharynx (Figure 1.5) (2).

Figure 1-5 CHANGES OF INTRA-ORAL PRESSURES DURING THE ORAL PHASE OF SWALLOWING.

These include the: (1) Oral preparatory phase, represented by the preparatory phase in the figure, and (2) Oral phase, represented by the primary propulsive and intermediate phases, with the terminal phase indicating the return to pre-swallowing pressures (58).

The soft palate becomes rigid via the contraction of the tensor palati (innervated by CN V, trigeminal nerve) and is then elevated via the levator palati (innervated by CN X, vagus nerve) to close the nasal part of the pharynx against the posterior pharyngeal wall, known as velopharyngeal closure (75). The space between the soft palate and tongue base is consequently opened, allowing for bolus transport from the oral cavity to the pharynx (Figure 1.4 B) (45, 62).

1.1.3 Pharyngeal Phase

The pharyngeal phase is largely involuntary with the main function to ensure the airway protection during swallowing (76). The pharynx is between 12-14 cm in length and vertically spans from the base of skull to the upper border of the upper oesophageal sphincter (UOS) (77). The pharynx is commonly divided into three segments: (i) the nasopharynx, which extends from the base of skull to soft palate, (ii) the oropharynx, which extends from the soft palate to the pharyngoepiglottic fold, and (iii) the hypopharynx, which extends from the pharyngoepiglottic fold to the UOS (Figure 1.6) (78). The posterior nasal opening, soft palate, oral cavity, valleculae, epiglottis, laryngeal vestibule and posterior surface of the cricoid cartilage form the irregular shaped anterior wall of the pharynx, while the posterior wall is smooth and continuous (79). The irregular anatomy of the anterior pharyngeal wall results in asymmetrical pharyngeal pressure generation during swallowing (79, 80), which can vary between individuals based on anatomical differences. Reconfiguration of the pharyngeal and laryngeal structures occurs during swallowing in order to propel the bolus through the pharynx and UOS, while concurrently providing protection of the airway (81).

Figure 1-6 ILLUSTRATION OF THE PHARYNX WITH ITS THREE SEGMENTS: NASOPHARYNX, OROPHARYNX AND HYPOPHARYNX (82)

The pharyngeal phase of swallowing is a complex, pattern generated response that is triggered by multiple mechanisms (51, 76, 83). Specific sensory mechanisms initiate the pharyngeal swallow and modulate the pharyngeal response. Bolus properties from the oral phase, such as taste, temperature and volume can influence this modulation (45, 84, 85). The sensory areas responsible for the pharyngeal response include the soft palate, uvula, dorsal surface of the tongue, faucial pillars, pharyngeal wall, and the pharyngeal surface of the epiglottis (sensory information is largely transmitted by the tonsillar and lingual branches of CN IX, CN X, and with lesser extent by the maxillary branch [V2] of CN V and CN VII) (44, 45, 86). Sensory stimulation functions to initiate and modulate swallowing, receiving mechanical, chemical and thermal input via receptors (48, 73, 87-90) predominantly located in the posterior tonsillar pillar (64, 91, 92). Bolus position at the onset of the pharyngeal swallow has been shown to be highly variable in healthy participants (93-95). On VFSS, bolus position at the initiation of pharyngeal swallowing has been shown to be below the tongue base and mandibular ramus across bolus liquid consistencies and solid foods in more than 90% (n=175/195) of healthy participants (95). Thus, the location of the bolus is not the sole factor that initiates the pharyngeal response (93, 96, 97).

Following swallowing initiation, the pharyngeal phase involves an overlapping paired sequence of inhibition and activation of muscles of the palate, pharynx, larynx and oesophagus (34, 44, 98). Although there is a consistent sequence of neuromuscular activity based on electrophysiology studies following swallow initiation (34), the temporal sequence of swallowing has been reported to be variable, at least based on visual instrumental assessment (99-102). The complex interplay of pharyngeal reconfiguration with simultaneous contractile pharyngeal pressures create a pressure on the bolus (intra-bolus pressure) to drive bolus propulsion (61, 103). The mechanisms that assist with pharyngeal reconfiguration, including velopharyngeal closure, tongue base retraction, hyolaryngeal excursion and UOS opening and relaxation are considered crucial for effective and efficient bolus propulsion through the pharynx and UOS (103-107). Pharyngeal contraction, on the other hand, has only minimal contribution to the generation of bolus movement pressure but contributes to bolus clearance following propulsive pressure generation (5, 103, 108).

During velopharyngeal closure, the elevation of the soft palate is driven by the tensor and levator veli palatine and contraction of the lateral and posterior nasopharyngeal wall (via contraction of the superior pharyngeal constrictor) eliminating nasal regurgitation (50, 56, 77, 109, 110) and contributing to enclosure of the pharyngeal chamber assisting with bolus propulsion through the pharynx and UOS (105). The bolus is then propelled backwards to the

oropharynx through tongue base retraction via shortening of the external tongue muscles (hyoglossus and styloglossus, innervated by CN XII) pulling the tongue base posteriorly against the posterior pharyngeal wall (45, 78, 103, 111). The driving force of tongue base retraction is a well-recognised contributory mechanism for bolus propulsion (61, 103), evidenced by greater posterior tongue base pressures than the lateral pressures (80). Figure 1.7 illustrates the pharyngeal muscles that contribute to velopharyngeal closure and tongue base contraction.

Figure 1-7 LATERAL AND PARTIALLY OPENED POSTERIOR VIEW OF THE MUSCLES OF THE PHARYNX (79) .

Following velopharyngeal closure and tongue base retraction, the hyolaryngeal complex initiates superior and anterior movement, commonly referred to as hyolaryngeal excursion, (78, 112) to transiently reconfigure the larynx from a respiratory to a swallowing function and direct the bolus to the pharynx and UOS (113). The hyolaryngeal complex comprises of the hyoid, thyroid muscle, thyroid hyoid membrane, thyroid cartilage, cricothyroid membrane, cricoid cartilage, cricopharyngeus muscle, trachea and oesophagus (Figure 1.7) (112). The antero-superior hyoid displacement occurs through the contraction of the submental muscles (mylohyoid, geniohyoid and anterior digastric) and the remaining suprahyoid muscles (posterior digastric and stylohyoid muscles) (3, 51, 71). The geniohyoid muscle is considered to be the major contributory muscle for the anterior hyoid movement, whilst the mylohyoid muscle is considered to be the major contributory muscle for superior hyoid movement (114). The extent and velocity of hyoid displacement is affected by bolus type and volume (115-117). The larynx simultaneously moves superiorly towards the hyoid, which occurs through contraction of the suprahyoid muscles, the larynx, and the thyrohyoid muscle (118). The anterior and superior movement of the hyolaryngeal complex creates a larger hypopharyngeal space, which results in a pressure reduction in front of the bolus and a negative pressure gradient creating a suction effect that, along with the driving pressure from the tongue, results in bolus propulsion through the UOS (Figure 1.8) (109, 119-121).

Figure 1-8 LATERAL AND ANTERIOR-POSTERIOR VFSS IMAGES DURING PHARYNGEAL SWALLOWING WITH ADJACENT RECONSTRUCTION OF HYOLARYNGEAL ELEVATION AND UOS OPENING AND RELAXATION.

1 = Epiglottis, 2 = Laryngeal Vestibule, 3 = Arytenoid Cartilage, 4 = Oesophagus (9).

Following hyolaryngeal excursion, pharyngeal shortening, which narrows the pharyngeal lumen reducing the distance for bolus movement, and pharyngeal contraction, which provides a bolus clearing force, occur concurrently (5, 121, 122). Pharyngeal shortening occurs through contraction of the longitudinal pharyngeal muscles (palatopharyngeus, salpingopharyngeus and stylopharyngeus muscles (innervated by CN X)) (5, 78), and pharyngeal contraction occurs through the superior, middle and inferior constrictor muscles (innervated by the pharyngeal branch of CN X via the pharyngeal plexus) (5, 11, 74, 123, 124). As the bolus passes through the pharynx, high pharyngeal pressures have been recorded at the bolus tail (determined from a combined VFSS and P-HRM study) (121), which is supportive evidence for the function of the pharyngeal constrictors in bolus clearance towards the UOS (Figure 1.9)(5, 103, 108).

Figure 1-9 SCHEMATIC REPRESENTATION OF THE COORDINATED RELAXATION AND CONTRACTION PRESSURES OF THE PHARYNX AND UOS.

At the UOS: a continuous basal pressure prior to swallow initiation, with a decreased in UOS pressure time (duration) and the relaxation pressure represented; followed by an increase in UOS pressure. At the pharynx, the increase pressure is shown from the beginning of the pharyngeal contraction wave with a peak (maximum pressures), followed by a decrease in pressures leading to the end of the pharyngeal contraction. Note the UOS relaxation occurs just prior to beginning of the pharyngeal contraction (125)

During hyoid elevation the epiglottis simultaneously inverts (126), sealing the laryngeal vestibule and directing the bolus away from the larynx and to the UOS (Figure 1.8) (127, 128). The laryngeal vestibule, an air-filled cavity, is anatomically defined superiorly by the free margins of the epiglottis, aryepiglottic folds and the arytenoid; anteriorly by the posterior region of the epiglottis; laterally by the thyroid cartilage and aryepiglottic folds; and inferiorly by the thyroarytenoid muscle (Figure 1.10) (129).

Figure 1-10 POSTERIOR VIEW OF THE LARYNX.

Anatomical regions are shown, E = epiglottis, AE = Aryepiglottic Fold, A = Apex of Arytenoids, Ventr = Ventricular Fold, VF = True Vocal Fold, PR = Pyriform Recess, SG = Subglottic Area. Sensory innervation of these regions are shown: iSLN = internal Superior Laryngeal Nerve and RLN = Recurrent Laryngeal Nerve (130).

Epiglottic inversion is primarily considered a biomechanical result of laryngeal elevation and tongue base retraction, with hyoid displacement having a minor contribution (Figure 1.8) (131, 132). Maximum epiglottic inversion occurs through the anterior tilting movement of the arytenoids, which allows for the contraction of the aryepiglottic muscle leading to adduction of the aryepiglottic folds, which further aids in airway protection (129, 133). Another airway protection mechanism contributing to airway closure is true vocal fold closure and close approximation of the ventricular folds (129, 133), which occur via contraction of the intrinsic laryngeal muscles, including the lateral cricoarytenoid and transverse arytenoid muscles that are innervated by the recurrent laryngeal nerve of CN X (Figure 1.7) (73, 134-136). The onset of true vocal fold closure has been reported to follow initiation of hyoid displacement, prior to maximum epiglottic inversion (133). Whilst these laryngeal events resulting in transient laryngeal closure are widely accepted, there are contradictory reports regarding the sequence of events (127, 128, 133). Regardless, accompanying this sequence of events, brief cessation of breathing during swallowing occurs with a duration ranging between 1 to 3.5 seconds (137-140). This is most commonly observed to interrupt exhalation, with completion of exhalation taking place after the pharyngeal phase of swallowing (138, 139).

In the event that food or fluid enters the larynx, the laryngeal adductor and cough reflexes are the fundamental airway protective mechanisms that are triggered (141-145). These reflexes can activate following mechanical and chemical stimuli via afferent fibres of the recurrent laryngeal nerve of CN X (143, 144, 146, 147). Sensory innervation of the true vocal folds and the laryngeal vestibule is via the internal branch of the superior laryngeal nerve of CN X, and the subglottic area is via the recurrent laryngeal nerve of CN X (Figure 1.10) (148). Following stimulation, the laryngeal adductor reflex results in bilateral vocal fold adduction that temporarily closes the glottis (130, 147). The cough reflex involves an initial inspiration, followed by forceful exhalation against adducted vocal folds causing increased subglottic pressure and a reduced tracheal size, and terminates with the opening of the glottis with explosive vigour to expel the material (146, 149).

After laryngeal mechanisms direct the bolus away from the larynx, it travels to the UOS, also known as the pharyngoesophageal segment, which separates the pharynx from the oesophagus (79). The UOS comprises of the cricopharyngeus muscles, cervical oesophageal fibres and oblique thyropharyngeal fibres of the inferior pharyngeal constrictor (Figure 1.7) (150, 151). Of these muscles, the cricopharyngeus muscles primarily contribute to changes in UOS pressures during swallowing (152). The pressure generation at the UOS is asymmetrical, due to

the asymmetrical anatomy of the UOS, with higher pressure generation in the anterior-posterior direction (153).

Bolus movement through the UOS to the oesophagus is facilitated by coupled changes in UOS pressure and opening, which are initiated early during swallowing prior to pharyngeal contraction (Figure 1.11)(154-156).The progression of UOS opening and bolus movement through the UOS includes the following sequence: (1) prior to the antero-superior movement of the hyolaryngeal complex, the UOS is contracted at rest (79, 157); (2) during hyolaryngeal excursion, an increased pressure on the UOS occurs as the hyolaryngeal complex pulls on the UOS, initiating UOS opening (105, 133) represented by sub-atmospheric pressures (158); (3) UOS relaxation ensues, through the relaxation of the cricopharyngeus muscle (via inhibition of the pharyngeal plexus and recurrent laryngeal nerve of CN X), over a duration of approximately 0.5 seconds (150); (4) the UOS elevates approximately 2-2.5 cm, termed the UOS apogee (highest point) (150, 159); (5) as the bolus moves through the opened UOS with resulting muscle force against the bolus producing an intra-bolus pressures, which widens the UOS further (158); (6) As the bolus passes, UOS distension pressure reduces. This leads to contraction of the pharyngoesophageal segment muscles, which closes the UOS lumen causing a transient rise in UOS pressures; (7) UOS pressures then return to pre-swallow baseline (104, 152, 154, 160-163); (8) as the bolus moves through the UOS, UOS contraction and the descent of the hyolaryngeal complex function to assist in bolus propulsion to the oesophagus and prevent regurgitation and aspiration (164).

Figure 1-11 IN THE VFSS IMAGE AT THE TOP, THE UOS MOVEMENT RELATIVE TO THE HYOID IS SHOWN.

The white arrows represent the direction of movement of the hyoid and the UOS sphincter. Sideways arrow = static (no changes), Downwards arrow = decreasing, and upwards arrow = increasing. In the diagram at the bottom, changes of UOS pressure and opening diameter during swallowing are illustrated. (154).

1.1.4 Oesophageal Phase

The oesophageal phase of swallowing is initiated when the bolus arrives at the oesophagus, and terminates once the bolus passes through the lower oesophageal sphincter (76). The oesophagus is a flattened muscular tube ranging between 18-26 cm and can be divided into three regions: the (1) cervical, (2) thoracic, and (3) abdominal regions (165). The proximal

aspect of the oesophagus consists of striated muscle, whereas the distal region consists of smooth muscle. The transition area between the striated and smooth muscle, known as the transition zone, constitutes both striated and smooth muscle and is approximately 4-8 cm in length (166). At rest, the upper and middle oesophageal regions are collapsed, whilst the distal region is rounded with no tone or rhythm activity (34).

Bolus flow along the oesophagus is characterized by bolus deceleration, stasis, and then acceleration again. Pharyngeal peristaltic contractions stimulate primary oesophageal peristalsis through innervation by vagal fibres of CN X (167). This sequential peristaltic pattern responsible for bolus propulsion through the oesophagus occurs through the activity of the two perpendicular opposing oesophageal muscular layers: an external layer of longitudinal fibres and internal circular muscle fibres (165). Propagation occurs down the oesophageal length: the oesophagus dilates distal to the bolus via contraction of the longitudinal muscles and relaxation of the circular muscles (167, 168). The proximal oesophageal region has significantly shorter swallowing reflex latency than the distal oesophageal region (169), indicating that afferent nerves are more superficial in the mucosa of the proximal oesophagus, than the lower oesophagus (170). When the bolus reaches the distal oesophagus, it triggers inhibitory feedback mechanisms to the smooth muscles in the lower oesophageal sphincter (LOS) causing relaxation. This allows the LOS to open and the food bolus to pass into the stomach. Once the bolus is in the stomach, the LOS returns to a high pressure zone, which functions to prevent reflux of the stomach contents (34). Oesophageal transit time differs depending on fluid consistency, ranging between 10-29 seconds (39).

Pharyngeal mechanisms have been shown to determine the extent of propulsion of the bolus into the oesophagus before peristaltic contribution takes over (171). Effectiveness of oesophageal contractility is dependent on the frequency of pharyngeal swallows (172). These findings suggest that the pharyngeal and oesophageal phases of swallowing are not completely separate entities and that some interaction likely exists between pharyngeal swallowing manoeuvres and oesophageal motility (173-175).

> *Overall, the physiological act of swallowing requires the sequential coordination of both voluntary and reflexive contraction and relaxation of many muscle groups for efficacious bolus transport to the stomach (36). The four-stage model of swallowing has been outlined with a description of each of the phases: oral preparatory, oral, pharyngeal and oesophageal (45), including anatomical descriptions of pertinent*

muscle groups and associated cranial nerves (V, VII, IX, X, and XII)(37). The delicate coordination of these cranial nerves through additional neural control mechanisms for swallowing are important to understand and are described in the following Section, Neural Control of Swallowing.

1.2 Neural Control of Swallowing

The neural control of swallowing is complex and multi-dimensional, and involves: (1) peripheral control, which influences and modulates the swallow through the sensory and motor functions of the cranial nerves, (2) brainstem control, which occurs through a central pattern generator (CPG) for swallowing that is located in the brainstem and functions to coordinate a stereotyped sequential motor activation and swallow pattern, and (3) cortical control, which includes cortical and subcortical brain regions and has an important role in the initiation and coordination of the swallow (34, 41, 44, 176-178). A brief review is outlined and represented in Figure 1.12 below.

Figure 1-12 MULTI-DIMENSIONAL NEURAL SCHEME REPRESENTATIVE OF THE OROPHARYNGEAL SWALLOW AND PRIMARY PERISTALSIS IN THE OESOPHAGEAL PHASE OF SWALLOWING (177)

1.2.1 Peripheral Control of Swallowing

The peripheral nervous system plays an integral role in swallowing. Although the CPG is somewhat autonomous in its sequential response, it depends on sensory input from cranial nerves for both the initiation and modulation of the swallow as outlined in Figure 1.12 (34). Afferent inputs from cranial nerves transmit mechanical (tactile, proprioceptive, tension), thermal, and chemical information to their brainstem relay nuclei, often converging in the solitary tract and ending in the nucleus tractus solitarius (NTS) (34, 48, 179). This can result in activation or modulation of the swallowing CPG, where there is accommodation of the efferent motor response according to the bolus characteristics (34, 180, 181). For instance, modulation of the pharyngeal swallow motor pattern, such as reconfiguration of the duration and pressure exerted by the pharyngeal and UOS surfaces to allow for adequate bolus accommodation, has been demonstrated in response to different bolus volumes, consistencies and textures in healthy participants through videofluoroscopic, manometric and surface electromyography studies (85, 99, 100, 102, 104, 159, 180, 182-188). Increased bolus volumes have been shown to result in increased lingual pressure (186), earlier onset of hyoid anterior and superior movement (159, 187), increased pharyngeal transit (85, 182, 184), earlier UOS opening (85, 104, 159), and increased UOS opening extent and duration (85, 104, 106, 159, 182, 184, 189). Although increased liquid viscosity has been less consistently reported to modify bolus accommodation when compared to increased volume (190, 191), it has been associated with

increased tongue pressure (188), increased pharyngeal transit (185), earlier hyoid movement (117), increased pharyngeal pressure (159) and prolonged UOS opening (192).

Multiple cranial nerves have important sensory and motor functions in the peripheral control of swallowing (76) and have been described with their specific function in *Section 1.1*. The following provides an overview of the neuroanatomy of these structures. The cranial nerves are organised in columns in the tegmentum of the brain stem. This forms the core of the brainstem with the cranial nerve cell bodies in either the floor of the IV ventricle or in the reticular formation (64). The medulla contains the pyramidal decussation, where motor efferents that originate in one cerebral hemisphere cross to the contralateral side (193). The motor nuclei associated with swallowing that emerge from the pons include the trigeminal (CN V) and facial nerves (CN VII); whereas the glossopharyngeal (CN IX), vagus (CN X), accessory (CN XI) and hypoglossal (CN XII) nerves emerge from the medulla (193).

The trigeminal nerve (CN V) contains both sensory and motor fibres. It has three branches: opthalmic and maxillary, containing sensory fibres, and the mandibular branch with mixed sensory and motor fibres (64). The facial nerve (CN VII) has both sensory and motor fibres and divides into five branches: the temporal, zygomatic, buccal, marginal mandibular and cervical branches (194). The glossopharyngeal (CN IX) is a mixed sensory-motor cranial nerve. The motor efferent pathways originate from two nuclei of the medulla: the parasympathetic nuclei, also known as the salivary inferior nucleus, and the visceral efferent from the nucleus ambiguous. The pharyngeal branch of CN IX joins the pharyngeal plexus (CN IX, X and XI via X). The vagus nerve (CN X) is a mixed sensory-motor nerve and innervates smooth, skeletal and cardiac muscle (194). CN X originates from the posterior cranial fossa and has six branches: auricular, carotid body, pharyngeal, superior laryngeal, cardiac and recurrent laryngeal. The accessory nerve (CN XI) is a somatic nerve that consists of spinal and cranial portions. The spinal portion contains somatic motor fibres that arise from the nucleus in the ventral horn of C2 - C4 roots. The cranial portion contains general visceral efferent fibres originating from the nucleus ambiguous, and joins the visceral efferent fibres of the vagus nerve. The hypoglossal nerve (CN XII) has a solely motor function. It carries the fibres of the superior root of the ansa cervicalis, which is a loop of nerves that are part of the cervical plexus (37, 194).

1.2.2 Brainstem Control of Swallowing

The brainstem control of swallowing is coordinated by functional circuits of interneurons, which are collectively known as the central pattern generator (CPG) of swallowing (33). Whilst cortical, subcortical, and peripheral inputs can influence the initiation and modulation of a swallow, the CPG of swallowing coordinates a timing pattern and a predictable and replicable motor swallow sequence independent from sensory feedback (Figure 1.12)(86, 195, 196). A CPG for swallowing was first proposed in early work by Meltzer (33) and is still widely accepted in contemporary literature. Current understanding is largely based on experimental microelectrode, lesion and anatomic tract tracing animal studies, however consensus has not been reached as to the exact location of the swallow interneurons (34, 197-201). CPG control mechanisms have also been identified in other coordinated processes, such as locomotion, mastication, respiration and cardiovascular regulation; the latter systems having neurons that share the same medullary sites as the swallowing neurons (202, 203). The shared pools of interneurons (also known as premotor neurons), which can also serve other central networks, enable the patterned swallowing response to occur in coordination with associated systems, such as respiration and mastication (34, 44, 193, 203-205). The swallowing CPG consists of two hemi-CPGs, which are located on each side of the medulla oblongata. It involves several brainstem motor nuclei and is formed by two main groups of interneurons: (1) the dorsal swallowing group (DSG), which is positioned within the nucleus tractus solitarus (NTS) and the adjacent dorsal medullary reticular formation, and (2) the ventral swallowing group (VSG), which is positioned in the ventrolateral medulla adjacent to the nucleus ambiguous (34, 195, 206). The two hemi-CPGs closely synchronise the coordinated bilateral contraction of the striated oral, pharyngeal and oesophageal muscles. The pharyngeal swallowing motor sequence is mostly generated in the ipsilateral hemi-CPG, which transfers the swallowing pre-motoneuron signals to the contralateral CPG (34, 207).

The DSG is located within the NTS, a primary sensory relay, and the interneurons in the DSG primarily receive and integrate sensory information (198, 208, 209). The NTS, specifically the intermediate, interstitial and ventral NTS subnuclei, is the principal sensory nucleus of the pharynx and oesophagus (76, 196, 201, 208). As depicted in Figure 13, the trigeminal (CN V), glossopharyngeal (CN IX) and vagus (CN X) nerves transmit peripheral sensory input to their brainstem relay nuclei to the NTS (124). Electrical stimulation studies in animals have shown that the superior laryngeal nerve (SLN) branch of the vagus nerve (CN X) and the pharyngeal branch of the glossopharyngeal nerve (CN IX) activate the interneurons in the DSG with the

shortest latency compared to other interneurons in the brainstem (76, 195, 205). Neurons in the DSG are responsible for the generation, coordination and timing of the sequential swallow pattern (34, 44). The output of the DSG is then projected to the VSG, also shown in Figure 4 (33). The VSG interneurons distribute this output to the numerous pools of motoneurons (34, 195), such as the nucleus ambiguous (NA), which comprises of the motoneurons of the glossopharyngeal (CN IX) and vagus (CN X) nerves that innervate the striated muscles of the pharynx, larynx and oesophagus (198, 204, 206); the trigeminal (CN V), facial (CN VII), and hypoglossal (CN XII) cranial nerves; the cervical spine neurons (C1 and C3); and the dorsal motor nucleus of the vagus nerve (CN X) which is responsible for the motor output of the distal oesophagus (195, 208). The activations of the VSG interneurons, when compared with the DSG interneurons, are considered to have greater overlap and increased latency and variability, suggesting greater polysynaptic connections (60, 198, 209). The VSG interneurons are also known as 'switching' neurons, as they are considered to contribute to the timing of activation of the motoneurons during swallowing (204).

There is suggestion that the pons and the cerebellum have a functional role in swallowing due to the close anatomic proximity and connectivity to the swallowing-related areas in the medulla in the brainstem (210-212). However, their exact role or extent of involvement are uncertain.

1.2.3 Cortical Control of Swallowing

The cortical and sub-cortical structures have a crucial role in the initiation and regulation of swallowing, which modulate the brainstem motor pattern (Figure 1.12)(213). Significant advancements in functional brain imaging techniques over the past decade have identified the cortical and sub-cortical structures activated during swallowing (41, 176). However, the specific structures involved and their significance for swallowing input remain poorly understood (214). Currently, it is largely accepted that the neurophysiology of swallowing involves multiple levels of the brain including the cortex, subcortex, cerebellum and brainstem that modulate one another (176, 215, 216). The main cortical and subcortical areas active during swallowing include: the sensorimotor cortex, sensorimotor integration areas, the insula and frontal operculum, the anterior cingulate cortex, supplementary motor areas, cuneus, precuneus, temporal lobe, orbitofrontal cortex, cerebellum, and less frequently reported: the posterior

cingulate cortex and basal ganglia (214, 217-219). Although the grey matter of these structures has been the focus of research in the cortical control of swallowing, there is emergent interest in the function of white matter (220).

The cortical and subcortical structures activated are distinct during reflexive and voluntary swallowing. Reflexive swallowing results in bilateral activation of the primary somatosensory and motor cortices (221). In contrast, volitional swallowing requires initiation and execution of the swallowing act as well as cue recognition and planning of the event (221). During voluntary swallowing, activation of the intermediate and caudal anterior cingulate cortex and the lateral aspect of the insula and the swallowing CPG in the brainstem occurs (218). However, the potentials required to initiate a voluntary swallow differ between individuals (222, 223), and are attributed to differences in activation in these cortical regions (35). Further, variability in voluntary swallow initiation is speculated to be associated with the chemosensory input transmitted via the supramedullary neural mechanism. However, the extent to which the supramedullary neurons, peripheral input and brainstem neurons contribute remains unknown (222).

Although the exact role of sensory input required by the cortical system during volitional swallowing remains unknown, it is recognised to have an important modulatory function in cortical control of swallowing, (176, 181, 224-227). Neuroimaging of human swallowing can determine specific activated brain regions in response to peripheral sensory stimulation associated with swallowing (181). For example, water infusion to the hypopharynx was shown to activate the caudolateral sensorimotor cortex, which is important for the initiation of the swallow; and volitional tongue movement was shown to activate more superior regions in the sensorimotor cortex (225).

The neural control of swallowing is complex and multi-dimensional. It involves peripheral, brainstem and cortical mechanisms (34, 41, 44, 176-178). Whilst cortical, subcortical, and peripheral inputs can influence the initiation and modulation of a swallow, the brainstem output coordinates a timing pattern of a predictable motor swallow sequence independent from sensory feedback (86, 195, 196). This neural control is required for the sequential coordination of both voluntary and reflexive contraction and relaxation of 26 pairs of muscles of the oral, pharyngeal and

oesophageal phases of swallowing (36). Impairment of any component of this complex system can result in dysphagia.

1.3 Epidemiology of Dysphagia

Dysphagia derives from the Greek word dys meaning disordered, and phago meaning to eat or swallow (177). Dysphagia is recognised by the World Health Organization (228) as a medical disability of the digestive system. It is categorised as either: (1) oropharyngeal dysphagia, which is associated with pharyngeal and/or upper oesophageal sphincter dysfunction, or (2) oesophageal dysphagia, which is due to oesophageal dysfunction (229). Oesophageal dysphagia is beyond the scope of this review and thesis and will, therefore, not be further explored. Oropharyngeal dysphagia is defined as the aberrant disruption of the motor and/or sensory function of the upper aerodigestive tract (9), which manifests as a disturbance of the oral and/or pharyngeal phases of swallowing (22). The causes of oropharyngeal dysphagia can be broadly classified into groups according to the underlying pathology, including mechanical, iatrogenic, infectious, neuromuscular or neurological causes (9, 37). Clinical observations of oropharyngeal dysphagia may present with symptoms such as liquid or food spillage from the lips, drooling, nasal regurgitation, coughing and/or regurgitation. Additional indirectly observed symptoms suggestive of oropharyngeal dysphagia include weight loss, repeated aspiration pneumonia, prolonged meal durations, sensation of food/fluids sticking in the throat and avoidance of certain food/fluid consistencies (22).

Dysphagia is associated with a range of comorbidities, including malnutrition, dehydration and aspiration pneumonia (230-234). These can lead to adverse health outcomes, affect quality of life for the individual diagnosed with dysphagia and their carer, and contribute to increased health care utilisation, which also significantly adds to health care costs (235-240). For example, in-hospital mortality associated with aspiration pneumonia ranges between 23-52%(241). In a recently published systematic review, an inverse bidirectional relationship was established between increased dysphagia severity and decreased quality of life (239). In a large study of heterogenous patients with dysphagia (n=360), 41% reported anxiety or panic during meal times and 36% reported social isolation during meal times (242). Malnutrition and dehydration are associated with increased hospital length of stay and known to contribute to increased health expenditure (8, 243, 244). In a systematic review, patients with oropharyngeal dysphagia experienced a 40% increase in health care costs compared to patients without dysphagia, with longer hospital length of stay a contributing factor (8).

The overall prevalence of oropharyngeal dysphagia has been reported to range between 6-50% (7). In the US, 1 in every 25 adults reported dysphagia symptoms (Bhattacharyya, 2014). In

Australia, 16% of the general population had experienced dysphagia symptoms in the previous 12 months (6). However, challenges exist in obtaining consistent and precise epidemiological data. This may be because dysphagia is not a distinct disease but rather a symptom associated with a wide range of underlying pathologies across the lifespan. Furthermore, there can be inconsistencies in definitions, as well as the timing and type of swallowing assessment that are utilised (7, 245). Dysphagia may present with differing severity and permanence, depending on the aetiology (246).

A higher prevalence of dysphagia has been identified in particular population groups. Sub-clinical dysphagia is a recognised morbidity associated with obstructive sleep apnoea (OSA) (247) and following the surgical management of OSA (248, 249). A high prevalence of oropharyngeal dysphagia has also been reported in the critically ill following extubation (250, 251) and following head and neck cancer treatment (252-254). These population groups will be explored in more detail in the following sections.

1.3.1 Obstructive Sleep Apnoea

Obstructive sleep apnoea (OSA), also known as Obstructive sleep apnoea syndrome (OSAS) is a chronic sleep-related upper respiratory condition (255). It is characterised by repetitive partial or complete upper airway collapse during sleep resulting in obstruction of breathing and arousal from sleep (256). Hypopnoea and apnoea episodes are defined by reduction and cessation of airflow, respectively. The prevalence of moderate OSA ranges between 1-17% in the general population (257, 258). OSA is strongly associated with the male gender, obesity (259) and aging (260). Undiagnosed OSA remains an ongoing health issue (261) and carries significant morbidity associated with excessive daytime sleepiness, impaired quality of life and work productivity (262-264), increased cardiovascular morbidity and mortality and motor vehicle accident risks (265).

The pathophysiological mechanisms that contribute to OSA are considered multifactorial, however they are not completely understood (266, 267). It is widely accepted that skeletal and soft tissue anatomical factors result in upper airway narrowing, collapsibility and obstruction (268). However, there is increasing evidence that additional mechanisms contribute to the pathogenesis. The low-frequency vibrations that occur with snoring and the tissue stretching that occurs with repeated pharyngeal collapse episodes can result in chronic inflammation and associated oedema of the pharyngeal soft tissue (266, 269, 270). This can lead to

neuromuscular changes of the upper airway, including peripheral afferent and efferent neural injury and muscle fibre alterations, such as axonal loss, increased connective and muscle fibre size, and fibre atrophy (271-273).

Dysphagia is a recognised comorbidity associated with OSA, with a prevalence ranging between 16-78% (247). Key abnormal bolus flow findings have been identified in patients with OSA and are representative of the subclinical presentation of dysphagia (274-276). In a recently published systematic review analysing OSA and swallowing function, the most common swallowing impairments reported were premature spillage and/or delayed swallow initiation, followed by observed penetration and pharyngeal residue (247). Although the mechanisms contributing to dysphagia in patients with OSA are not well established (247, 276), neural injury causing sensory impairment and peripheral disturbances in pharyngeal swallowing has been hypothesised (272, 274, 277-279). Further research is required to understand the contributing mechanisms to the pathophysiology of dysphagia associated with OSA, which will be explored in this thesis. Additional information is provided in *Chapter 4*.

1.3.2 Surgical Management of Obstructive Sleep Apnoea

Surgical intervention for the management of OSA was first described 30 years ago (280). Over this time, there have been advancements in surgical techniques to remodel the airway at identified anatomical regions of collapse (281, 282). Although medical management of OSA, such as continuous positive airway pressure (CPAP) therapy, is considered the first line treatment for maintaining airway patency (256), reduced adherence and/or tolerance (283, 284) impedes the possible health benefits (285). Accordingly, surgical management for OSA is an accepted alternative treatment following failure of CPAP therapy (286).

Uvulopalatopharyngoplasty (UPPP) followed by radiofrequency of the soft palate and tongue base are the most commonly performed surgical procedures in the management of OSA (287). An adapted UPPP technique, known as modified UPPP (mUPPP), minimises excess tissue removal of the velopharynx and uvula to optimise outcomes and reduce associated surgical morbidity (288). Tongue coblation or channelling technology (CCT; radiofrequency and saline) ablates tissue columns reducing tongue volume (288). At our centre, mUPPP with bilateral tonsillectomy with or without CCT is the multi-level surgery offered to patients with OSA who are non-compliant with medical device use. Recently in a randomised controlled trial, this

contemporary surgical technique has been reported to reduce the severity of OSA as well as day-time sleepiness (281).

Dysphagia has been identified following the surgical management for OSA, with a reported incidence of 18-27% (248, 249). This has been observed to be either transient (286, 289-291) or persistent (1, 292-295). Swallowing function during post-surgical evaluation has most often been assessed using self-reported outcomes (287, 292, 293, 296-311). These studies have not utilised validated patient reported outcome measures of swallowing. VFSS has been the visual instrumental assessment utilised to assess post-surgical pharyngeal swallowing function (290, 294, 295, 312-315). From the seven studies that conducted a VFSS, one study did not find significant differences in hyolaryngeal function pre- and post-surgery (314). Five studies noted post-surgical swallowing abnormalities identified with VFSS, including premature spillage, pooling in the vallecula, incomplete epiglottic inversion, nasopharyngeal regurgitation, reduced tongue base retraction, reduced pharyngeal shortening, laryngeal penetration and aspiration, pharyngeal residue, increased hyoid and velum movement times and increased pharyngeal transit times (290, 294, 295, 312-315). Further research is required to prospectively evaluate swallow function pre- and post-upper airway surgery to expand current understanding of the impact of contemporary surgery on swallowing. This will be investigated in this thesis. Additional information will be provided in *Chapter 5*.

1.3.3 Critically Ill Following Extubation

Endotracheal intubation (ETI) is a commonly performed procedure in critically ill patients (316) that involves the placement of an artificial tube through the vocal folds and into the trachea to protect the airway and facilitate lung ventilation (317). Dysphagia is frequently reported following the removal of an endotracheal tube, which is referred to as post-extubation dysphagia (PED)(250, 251, 318). A recent systematic review found that 41% of the critically ill population have PED (250), although the literature reports significant variation in the reported incidence in this patient group, between 3-93%, likely attributed to the timing, type of swallow assessment and population heterogeneity (251). PED is recognised as an independent risk factor for increased mortality (319-322) as well as increased morbidity requiring higher resource use (251), including increased ICU and overall hospital length of stay (321-323). It is well known that ICU provide for complex intensive and invasive care with higher associated costs (324-327), which is estimated to be between 1-12% of the total annual health care costs (324, 325).

Visual instrumental swallow assessments, videofluoroscopy swallow study (VFSS) and fibreoptic endoscopic evaluation of swallowing (FEES), have largely reported aspiration status as a key outcome measure in critically ill patients following extubation (328-332), with identified mechanisms including increased bolus time in the hypopharynx prior to swallow initiation (329, 330), incomplete epiglottic tilting (329), increased time of laryngeal closure and shorter pharyngoesophageal segment opening (333). Primarily due to patient transport requirements external to the ICU, VFSS swallowing assessment is not considered to be feasible in the critically ill, with swallow assessment by the bedside being more suitable (330, 331, 334). Consequently, few studies have investigated swallow function using VFSS alone in critically ill patients following extubation (319, 323, 328, 329, 333-337), with FEES being the most commonly utilised visual instrumental assessment for this patient group (330, 331, 337-343).

Prolonged endotracheal intubation, defined as >48 hours, is a widely reported risk factor in the development of PED (318-320, 323, 330, 331, 335, 336, 342-346), although not all studies have found this association (333, 338, 340, 341, 347). Intubation duration of 6 or more days has been associated with increased incidence and severity of dysphagia, as well as self-reported dysphagia symptoms at hospital discharge (328, 346, 348). The pathophysiological mechanisms contributing to dysphagia in the critically ill are not well established but appear to be multi-factorial (46, 251, 349, 350), with iatrogenic aetiology (such as injury associated with tube misplacement), neuromuscular weakness, reduced laryngeal sensation and impaired cognition considered key factors (46, 349, 351). Further research is required to determine the key swallowing mechanisms that are altered following extubation that contribute to dysphagia, which will be examined in this thesis. Additional information will be provided in *Chapter 7*.

1.3.4 Post Head and Neck Cancer Treatment

Head and Neck Cancer (HNC) is the sixth most common cancer (352) and comprises of a group of cancers of the oral cavity, pharynx, larynx, paranasal sinuses, nasal cavity, salivary glands and head and neck lymph nodes (353). Approximately 90% of these are squamous cell carcinomas (SCC) arising from the mucosal surfaces (354). Risk factors of head and neck cancer squamous cell carcinoma (HNCSCC) are tobacco, alcohol (355) and viral carcinogenesis, specifically Epstein-Barr Virus (EBV) (356) and Human Papillomavirus (HPV) infection (357). HPV-positive associated oropharyngeal cancers have shown increased survival rates when treated with concurrent chemoradiation, resulting in a growing group of people

surviving HNC treatment (354, 358). The HNC diagnosis is derived from the tumour location and size, extent of lymph node involvement and presence of distant metastases (359). This classification broadly assigns early staged HNC (I and II) requiring single-modality treatment (360), and advanced staged HNC (III and IV) (360) requiring multi-modality treatment of surgery followed by radiotherapy or concurrent chemoradiation (361, 362). More than 60% of HNC patients present with advanced HNC (363) that necessitates radiation treatment as part of the oncologic treatment (364, 365).

Dysphagia is a common complication for patients with HNC and following HNC treatment (252, 254, 366, 367). The presence and severity of dysphagia varies depending on the location and size of the tumor, and the treatment modality utilised (253). At the time of HNC diagnosis the incidence of dysphagia ranges between 28-50% (368, 369). This is considered a consequence of the primary cancer altering the motor muscle movements and is associated with an increased prevalence of post-treatment dysphagia (367).

Dysphagia has been associated with radiation treatment, known as radiation-induced dysphagia (367), which comprises of mechanical, structural and neurological deficits (370). These injuries are classified according to time lapse following radiation: (1) acute (< 3 months), (2) sub-acute (3-6 months) and (3) chronic (> 6 months) (370, 371). The radiation field during radiotherapy treatment for HNC exposes muscles required for swallowing to radiation doses, in particular to the pharyngeal constrictors, larynx and cricopharyngeus (372). Acute radiation injury manifests as oedema, mucositis, pain and xerostomia (370, 371, 373), whilst chronic radiation injury manifests as muscle fibrosis and atrophy (370). Dysphagia is considered to result from reduced range of motion of the laryngeal and pharyngeal structures, which may be as a result of oedema in the acute setting, or fibrosis and neuromuscular weakness in chronic presentations (374, 375). Unfortunately, radiotherapy techniques, in an attempt to minimise the radiation dose delivered to identified key muscles necessary for adequate swallowing, have not been successful in minimising the prevalence of dysphagia (376, 377).

Multi-modality treatment for HNC (radiotherapy, chemotherapy and/or surgical resection) can result in acute and long-term dysphagia, which is negatively associated with health-related quality of life (378). The prevalence of dysphagia following multi-modality treatment was recently reported in a systematic review to be 45.3% (252-254). Following treatment, the prevalence of aspiration-related mortality is as high as 19-27% (379). VFSS has been primarily used to

recognise pathophysiological oropharyngeal swallowing changes following HNC treatment, with identified abnormalities including base of tongue dysfunction, reduced pharyngeal contraction, and reduced UOS opening (366, 380-388). Altered bolus flow outcomes of residue and aspiration have also been identified in VFSS and FEES studies following HNC treatment. Further research is required to understand the swallowing biomechanics following HNC treatment to gain broader insight into the alterations in swallowing function that contribute to dysphagia. This will be evaluated in this thesis. Additional information will be provided in *Chapter 8*.

> *Oropharyngeal dysphagia is a highly prevalent symptom following head and neck cancer treatment (252-254) and in the critically ill following extubation (250, 251); and is associated with obstructive sleep apnoea (247) and following the surgical management for OSA (248, 249). Accurate assessment methods are crucial to identify oropharyngeal dysphagia in these patients early to minimize the well-recognised comorbidities associated with dysphagia, including malnutrition, dehydration, and aspiration pneumonia (230); as well as the associated impact on diminished quality of life for both the individual with dysphagia and their carer (239, 389), and the associated health care utilisation and cost (8, 238, 243, 244). The following Section outlines the swallowing assessment techniques currently utilised in clinical practice to identify and diagnose oropharyngeal dysphagia.*

1.4 Swallowing Assessment

Speech pathologists are internationally recognised as the primary providers of oropharyngeal dysphagia assessment and management (25, 390-392). Common methods for the assessment of swallowing include: patient-reported outcome measures (PROMs) of swallowing, clinical swallowing examination (CSE), videofluoroscopic swallow study (VFSS), and fibreoptic endoscopic evaluation of swallowing (FEES) (Figure 1.13). Each of these methods will be discussed in more detail in this section. Although not represented in Figure 1.13, the use of PROMs has been included in this section because it is considered an invaluable aspect of the swallowing assessment from the patients' perspective (246, 393). The use of PROMs of swallowing as well as clinician-reported CSE findings have been advocated for during the assessment of dysphagia (22). CSE findings may precipitate further investigation utilising instrumental assessment. The appropriate selection and interpretation of the swallowing assessment is critical to identify the salient features of dysphagia, which then informs appropriate management planning across a wide spectrum of medical conditions or disease processes (22, 177, 394-398). As P-HRM is the swallowing assessment method utilised in each of the studies in this thesis, this technology will be reviewed in depth in *Section 1.5*. Other modalities, including functional lumen imaging probe (FLIP) and accelerometry using cervical auscultation were considered outside the scope of this overview and will therefore not be further discussed.

Figure 1-13 OROPHARYNGEAL DYSPHAGIA DIAGNOSTIC MODALITIES.

Screening can identify patients at high-risk of dysphagia requiring clinical swallow assessment (in blue), which involves patient history, physical and oromotor exam and food/fluid intake assessment to identify aspiration risk and the possible site, severity and prognosis of dysphagia. Findings from the clinical swallowing assessment may determine whether an instrumental swallowing assessment (in purple) is indicated, such as Videofluoroscopy Swallowing Study (VFS), Fibreoptic Endoscopic Evaluation of Swallowing (FEES), High-Resolution Manometry (HRM), Functional Lumen Imaging Probe (FLIP) or Accelerometry (commonly termed cervical auscultation) (22).

1.4.1 Patient-Reported Outcome Measures of Swallowing

Over the past 30 years, the development of different PROMs of swallowing have provided methods to collect patient-centred outcomes which can be useful to understand patient experience, symptom severity, impact on quality of life (QOL), and as a means to evaluate

perceived treatment effectiveness (399). PROMs of swallowing may be classified as symptom scores which determine deterioration or improvement of symptoms in order to ascertain effectiveness of treatment, or quality of life (QOL) measures which determine the impact of swallowing dysfunction on QOL (246, 393, 399, 400). PROMs of swallowing are considered an important component of dysphagia assessment (22), with its feasibility being noted at the time of CSE and/or instrumental swallowing assessment (401).

Many PROMs of swallowing used to provide swallowing symptom scores have been reported and evaluated in the literature. While important information can be gathered, considerable disparity is recognised in the self-assessment of oropharyngeal dysphagia using PROMs of swallowing compared with instrumental swallowing assessment (389, 402-404). In one study, 76% of a heterogenous cohort in an outpatient setting were observed to have abnormal swallowing on instrumental swallowing assessment of VFSS and or FESS, yet most reported managing regular diet and fluids (402). While a poor correlation exists between aspiration and self-reports of oropharyngeal dysphagia (389), positive correlations have been found with abnormal pharyngeal residue (405). In several studies that utilised PROMs of swallowing as a QOL measure, no correlation was reported between abnormal oropharyngeal swallowing and instrumental assessment (389, 403, 404). Consequently, several studies have advocated for revised cut-off values in current PROMs of swallowing so greater correlation between dysphagia reports and instrumental assessment can be observed (402, 405, 406).

The discrepancy between PROMs of swallowing and instrumental swallowing assessments in dysphagia identification, as well as other factors such as poor patient cognition, advanced progression in degenerative diseases, and limited clinician time may all hinder the accurate completion of self-reported swallowing assessments (407), and may account for their limited use during routine clinical practice (408). While important information regarding patient experience can be obtained from PROMs of swallowing, particularly the impact of symptoms on QOL (404), they have limitations in providing objective information that can be generated using alternative swallowing assessment techniques.

1.4.2 Clinical Swallowing Examination

Clinical swallowing examination (CSE) involves the collection of the history and current presentation of dysphagia symptoms and general observations, consideration of the relevant medical and social factors, examination of oral motor and sensory cranial nerves and

observation of swallowing of liquids and solids (50, 60, 401, 409, 410). It is a non-invasive assessment method that can infer the presence, severity, and expected prognosis of oropharyngeal dysphagia and aspiration risk. Findings from CSE may determine whether an instrumental swallowing assessment is indicated (Figure 1.13)(25, 390, 391, 397). CSE is less disruptive to patients, is resource efficient (50), and is the most commonly utilised swallow assessment method by speech pathologists (411-413).

The noteworthy benefit of CSE has been demonstrated across various outcome measures, with significant correlations found with clinical outcomes, such as hospital length of stay, morbidity and mortality (320, 345); and with VFSS outcomes, including overall dysphagia severity (414). Specific measures examined during CSE, including dysphonia, abnormal laryngeal elevation during swallowing, abnormal volitional cough, cough with swallowing, and oxygen desaturation of 2% or more have demonstrated accuracy for the identification of increased risk of aspiration (415-418). The use of these measures, which have demonstrated increased validity and reliability, as part of CSE are recommended by the European Society of Swallowing Disorders (397). Employing a standardised approach to CSE, such as the validated Mann Assessment of Swallowing Ability (419), has shown a positive correlation with VFSS in patients with moderate-severe aspiration risk (420). A standardised CSE provides consistency with reported outcomes, which maintains clinical standards and offers advantages during broader evaluation of reported outcomes (401, 421, 422).

The inherent limitations of CSE in the provision of a complete dysphagia assessment are recognised, particularly as the pharyngeal and oesophageal phases of swallowing are not visible (423). When compared with instrumental swallowing assessments of VFSS or FEES, CSE has shown reduced accuracy in identifying key physiologic impairments and silent aspiration in approximately 20-40% of patients (414, 417, 424, 425). Furthermore, variable practise patterns during the CSE are acknowledged in the literature, raising concerns regarding the validity and reliability of reported measures (412, 426). Although increased reliability has been demonstrated when the same clinician conducts a CSE (412, 426), this decreases between clinicians (425, 427, 428), which could reflect the experience of the clinician (411, 429) and/or the clinical setting (430). While CSE is a critical component of dysphagia assessment, this method is limited when compared to instrumental assessments that provide visible outcomes of swallowing.

1.4.3 Fibreoptic Endoscopic Evaluation of Swallowing

Fibreoptic endoscopic evaluation of swallowing (FEES) was first introduced in 1988 (431, 432) and involves the insertion of a flexible laryngoscope trans-nasally to view the pharyngeal and laryngeal structures prior to, during, and post-swallowing (Figure 1.14)(431, 433). Additional features of this assessment include determining the amount, location and type of secretions, pharyngeal sensation, laryngeal sensation and response to visual biofeedback in attempts to modify swallowing behaviour (commonly termed biofeedback) (396, 432, 434-437). The most commonly reported measures used in FEES interpretation include: amount of secretions and/or residue, penetration and aspiration (394). As part of the FEES protocol, green or blue dye is mixed with the liquid and food based on the presumption that visualisation is enhanced against pharyngeal and laryngeal mucosa and oropharyngeal secretions (432, 438-440).

In contrast to VFSS, FEES provides the opportunity of portability allowing for the assessment to be conducted by the bedside without the requirement for radiation exposure and allows for repetition of assessments as well as use in biofeedback therapy (10, 441-443). Several limitations of FEES have been acknowledged, including a lack of consensus regarding the assessment protocol, which exposes the risk of inconsistencies during the assessment and in the interpretation of findings, as well as the extensive training requirements (444-448). Training of clinicians involves both the technical skill development for endoscope placement (449), which is critical in order to minimise procedural risks and reduce side effects (435, 450), as well as the training required for the reliable interpretation of assessment findings (10). For the interpretation, bolus type and consistency, residue severity, head positioning and frame rate of recorded images can influence the observations, which can result in variability of pharyngeal residue and aspiration ratings (440, 451-454). However, high inter-and intra-reliability agreement has been reported in the assessment of aspiration with the use of the Penetration-Aspiration Scale (PAS) (455), regardless of clinician experience (456); and in the assessment of residue using anatomical derived scales such as the Yale Pharyngeal Residue Severity Rating Scale (457) and the Mansoura Fibreoptic Endoscope Evaluation of Swallowing Residue Rating (458).

1.4.4 Videofluoroscopic Swallowing Study

Videofluoroscopic swallowing study (VFSS), also referred to as modified barium swallow (MBS), is considered the gold standard for the evaluation of oropharyngeal swallow function and the

assessment of penetration and/or aspiration (50, 459). It is a dynamic assessment of bolus flow when a patient is upright, enabling visualisation of 2-dimensional images of the oral cavity, pharynx and UOS (Figure 1.14) (460, 461). VFSS most commonly measures visual observations, including oral phase duration, timing of swallow initiation, pharyngeal phase duration, aspiration and pharyngeal residue (394). These observations inform the nature of the oropharyngeal dysphagia, whereby inferences can be made regarding the underlying oropharyngeal pathophysiology (50, 462). VFSS can be used to evaluate the effectiveness of management techniques, such as providing visualisation of compensatory manoeuvres during swallowing, and provides valuable information to inform treatment planning for dysphagia management (50, 463). A well-recognised disadvantage of VFSS is the exposure of the patient to ionizing radiation. However, the radiation dose associated with VFSS is modest and consistent with the As Low As Reasonably Achievable (ALARA) principle (464-467).

There are several recognised limitations of VFSS, including limited duration for assessment (to minimise radiation exposure), increased use of personnel and equipment resources, the requirement for the patient to be moved to the Radiology Suite for assessment, which can be disruptive for the patient or present a barrier if the patient is not clinically suitable for transfer (460), and variability associated with VFSS analysis and interpretation. High variability exists between clinicians in both the measurements that are used during the analysis of VFSS and in the interpretation of the measurements (394, 459, 463, 468-470) resulting in clinician's reliance on subjective interpretation (463). In a study that reported on survey results examining the accuracy of VFSS analysis by speech pathologists, an overall poor to modest agreement of impairment identification was found, with poorer agreement occurring with increasing dysphagia complexity (468). Furthermore, an overemphasis on the identification of bolus flow outcomes of penetration, aspiration, and residue rather than the identification of physiological impairments is a concern that has also been raised (468, 471, 472).

Marked progress in standardising the VFSS assessment has occurred since its introduction approximately 30 years ago (10, 60, 473). Importantly, the use of a standardised assessment protocol has not been associated with an increase of ionizing radiation time (474). Standardisation of multiple aspects of the VFSS assessment, including the bolus administration protocol, bolus contrast, acquisition frame rate, patient instructions, clearly defined ordinal visuo-perceptual and continuous temporal and spatial variables, and standardised reporting have been advocated for in the literature, with studies demonstrating improved intra- and inter-rater reliability (10, 60, 175, 459, 473, 475-478). Improved reliability and accuracy of VFSS

analysis have been found when clinicians are provided with standardised definitions of physiological impairment with quantified measures using nominal or ordinal scales (455, 479-483). Ordinal rating scales commonly reported in the literature include: the Penetration-Aspiration Scale (PAS)(455), which quantifies penetration and/or aspiration, and the Dynamic Imaging Grade of Swallowing Toxicity (DIGEST) (482). Additional to these rating scales, which can easily be incorporated within an established clinical service, specific software programs and training are available for the interpretation of VFSS. These software programs that provide a quantified measure of oropharyngeal dysfunction include: the Modified Barium Swallow Impairment Profile (MBSImp)(481), the Dynamic Swallow Study (60), and the Analysis of Swallowing Physiology Event, Kinematics and Timing for clinical application (ASPEKT-C) (94) with the normalised residue ratio scale (NRRS)(483). Despite the promising developments in standardisation, variability between clinicians in the VFSS measures that are used and in their interpretation remains. This may be, in part, due to the absence of a global set of standardised quantitative measures in VFSS analysis (10, 484).

1.4.5 Summary of Visual Instrumental Swallow Assessments

VFSS and FEES are visual instrumental assessments widely used for the assessment of oropharyngeal dysphagia (10, 22, 396, 485). Figure 1.14 displays simultaneous images of a FEES and VFSS during the same swallow. Whilst VFSS is considered the 'gold' standard in swallowing assessment, FEES has arguably demonstrated comparable validity (441). Several studies have compared the efficacy of VFSS and FEES in the assessment of penetration, aspiration and residue (339, 445, 486-490). There is debate in the literature regarding the sensitivity and specificity of the penetration, aspiration and premature spillage measures when comparing VFSS and FEES. Although some studies have demonstrated high-sensitivity and specificity (339, 486-489), others have reported an increased severity in rating of penetration, aspiration and/or pharyngeal residue when using FEES compared to VFSS (444, 445, 490-492). These findings could indicate that FEES is more sensitive in rating these measures compared with VFSS (487, 491, 492); or that FEES provides an overestimation on these measures (486). The demonstrated inconsistency of bolus flow outcomes illustrates that the assessment of oropharyngeal dysphagia may differ according to the choice of visual instrument and questions whether either is truly the 'gold' standard (488). Alternatively, these assessment methods may be referred to as reference standard tests. Currently, there is insufficient evidence identifying specific measures supporting valid and reliable interpretation of VFSS and FEES (394).

Figure 1-14 SIMULTANEOUS IMAGE OF FEES (LEFT) AND VFSS (RIGHT).

On the FEES image, the laryngeal surface of the epiglottis is shown (white arrows) with blue-dyed bolus observed anterior to the posterior pharyngeal wall (white star). The remainder of the hypopharynx is obscured during the swallow. On the VFSS image of the same swallow on the right, the star represents the same position of the posterior pharyngeal wall. The white arrow at the laryngeal vestibule demonstrates the aspects unable to be observed during the swallowing on a FEES that can be viewed during a VFSS. Please note the white arrow with a longer line highlights the endoscope at the velopharynx and the arrow without a line is highlighting the laryngeal penetration on VFSS unable to be viewed at the same time on FEES (490).

VFSS and FEES are both considered necessary for the identification of bolus flow abnormalities of aspiration risk and bolus residue; are useful to detect the effectiveness of management techniques (e.g. compensatory manoeuvres); and provide beneficial information that can be used to determine diet/fluids recommendations for the individual patient (10, 22, 396, 485). These visual instrumental swallowing assessments address the limitations of CSE that is unable to directly view the oropharyngeal and laryngeal structures. There is an ongoing need to develop internationally-agreed quantified and valid and reliable measures in both VFSS and FEES (10, 394, 484). However, the recognised limitations in visual instrumental swallowing assessment may simply emphasise the inherent limitations associated with the interpretation of visual observations endeavouring to measure the pressure-driven events of the oropharyngeal phases of swallowing (11). Thus, there is a need for alternative methods for further evaluation in the assessment of oropharyngeal swallowing, such as high-resolution pharyngeal manometry with impedance.

1.5 Pharyngeal High-Resolution Pharyngeal with Impedance

P-HRM-I is a trans-nasal catheter assessment of pharyngeal swallowing that provides objective and quantified data of pressure and bolus flow outcomes during swallowing. P-HRM/P-HRM-I has been gaining recognition over the past ten years (10, 22, 493-495) and is recognised by the American Speech-Language-Hearing Association (24) as an emerging area of practice for speech pathologists. In Australia, P-HRM-I is acknowledged as a swallowing assessment technique by Speech Pathology Australia (25), however there are currently no guidelines or recommendations regarding its application in clinical practice.

P-HRM involves data acquisition from closely spaced pressure sensors to measure the contractile activity representative of pressure generation spanning the pharynx to the UOS

(496). P-HRM-I simultaneously measures the pharyngeal and UOS contractile muscle activity (pressure generation) with intra-luminal impedance that is representative of bolus movement across time (21, 497-499). Together with analysis algorithms, these pharyngeal swallowing measurements allow for a sophisticated and quantifiable biomechanical assessment that ultimately increases the understanding of swallowing physiology and pathophysiology (10, 21, 500). P-HRM with or without impedance measures may be used in conjunction with VFSS, which is known as videomanometry (VM), or historically as manofluorography (11, 22, 31, 501, 502). Although VM is considered to provide enhanced interpretation of swallowing pathophysiology and ultimately treatment outcomes (503), further research is required to identify and correlate the key manometric and/or impedance measures with VFSS observations (31, 494, 504).

Currently, in the Gastroenterology field, HRM is considered the gold-standard diagnostic assessment of oesophageal motility disorders in clinical and research settings (18, 493, 505, 506). Unlike visual instrumental assessments, oesophageal HRM provides biomechanical measures of muscle pressure and relaxation (Figure 1.15) (507). HRM quantified metrics provide the definitions to categorise oesophageal motility disorders according to a hierarchical clinical algorithm, known as the Chicago Classification (508, 509), with version 4.0 being the most recently published (510). This algorithm assists in treatment planning and objective analysis of treatment outcomes (507, 511). Given that the pharyngeal and subsequent oesophageal phases of swallowing both function to propel the bolus to the stomach (35, 51), and pharyngeal mechanisms impact oesophageal motility (171, 173), there is merit in further evaluating the potential for P-HRM with or without impedance to provide a comparable gold-standard assessment for pharyngeal swallowing.

Figure 1-15 SALIENT PRESSURE MEASUREMENTS DURING HRM WITHIN THE OESOPHAGUS.

A. Opening pressure: as the oesophageal wall opens the falling pressure is recorded; B: Intra-bolus pressure (termed hydrodynamic pressure in the figure): as the bolus surrounds the catheter, the pressure within the bolus reflects the force that is applied to the bolus; and C: Contact pressure: the oesophageal muscles contract and compress the catheter and the rising pressures are recorded (158).

The accuracy of pressure measurement during swallowing may be affected by a number of factors, including: (1) catheter type (water perfused versus solid state); (2) pressure sensor

transducer configuration (unidirectional versus circumferential); (3) manometry catheter resolution (conventional versus high-resolution) (31, 507, 512); (4) individual pressure sensor variability (513-515); (5) the effect of the catheter presence itself on swallowing (516, 517); and (6) the administration of topical anaesthesia prior to catheter insertion (518). These factors will be further explored in the following sections.

1.5.1 P-HRM-I Considerations

1.5.1.1 Water-Perfused and Solid-State Catheters

A manometric catheter contains pressure sensors to detect contractility/pressure forces, which are transduced into electrical signals (507, 512) and recorded in millimetres of mercury (mmHg) (519). The pressure sensor and transducer components are interfaced with recording equipment that is able to record, digitise, display and store the signals (507, 520). The two manometric catheter options are: water-perfused catheters with external volume displacement transducers, or solid-state devices with electronic transducers; these substantially differ in terms of equipment costs and preparation, location of transducers and ability to detect a rapid pressure rise (17, 507).

Water-perfused systems operate via the continual perfusion of sterile water from a reservoir via a pneumatic perfusion pump, through multiple lumens along the manometric catheter, which are connected to external volume displacement transducers (Figures 1.16 and 1.17). Pressure changes are generated within the lumen and are transmitted back to the column of water to the external transducers in the perfusion pump (520, 521). Water-perfused catheters have widely spaced pressure sensors resulting in large areas of data being collected requiring a sleeve sensor to measure the highest pressure along a segment of several centimetres (Figure 1.16)(522). Although water-perfusion manometry incorporates low cost catheters when compared to solid state systems, multiple barriers exist for their application in clinical practice, including the requirement for increased expertise and time for equipment preparation (522), increased risk of hydraulic dampening reducing the accuracy of pharyngeal pressure measurement (31), and water infusion into the pharynx which may not be tolerated by patients (523), especially those with pharyngeal dysphagia who are at risk of aspiration.

Figure 1-16 DIAGRAM OF A SLEEVE SENSOR POSITIONED EXTERNAL TO THE WATER-PERFUSED CATHETER.

Water enters the sleeve channel proximally and exits distally (153).

Solid-state catheters comprise of internal micro-transducers of either metal diaphragm strain gauges or piezo-resistive silicon chips, which have a pressure sensitive area of $1mm^2$ (520). When pressure is applied on the metal diaphragm, the strain gauges or silicon chips transform the mechanical pressure to an electrical current (Figure 1.17)(520, 521). The reduction in pressure sensitive area size allows for an increase in the number of pressure sensors with condensed spacing, which enables an earlier response in pressure detection and circumferential changes (17, 521).

Figure 1-17 REPRESENTATION OF THE SOLID-STATE AND WATER-PERFUSED SYSTEMS.

a. Solid-state catheter: the signal from the catheter is directly digitised to a computer for acquisition and recording. b. Water-perfused system: a multi-lumen catheter is connected to the external transducer via the pneumohydraulic pump, which is then interfaced and the signal digitised to a computer for acquisition and recording (524).

1.5.1.2 Unidirectional and Circumferential Sensors

Water-perfused and solid-state catheters incorporate pressure sensors that may comprise of unidirectional transducers, measuring pressure from one direction, or circumferential transducers, measuring an average pressure from several points (Figure 1.18)(507). Although the clinical significance of the use of unidirectional compared with circumferential sensors has not been clearly established, the average pressure from the multiple transducers is a feature of circumferential sensors that is hypothesised to provide more accurate detection of pressure generation (521). This is particularly relevant given that pharyngeal and UOS regions have demonstrated asymmetrical pressures generation (31, 80, 153, 525).

Figure 1-18 MANOMETRY CATHETERS INDICATING THE CIRCUMFERENTIAL AND UNIDIRECTIONAL TRANSDUCERS THAT ARE INCORPORATED WITHIN EACH OF THE INDIVIDUAL PRESSURE SENSORS.

A. Solid state catheter with 12 circumferential transducers per sensor; B. Solid-state catheter with one single unidirectional transducer per sensor (526).

1.5.1.3 Conventional and High-Resolution Manometry

The density of the pressure sensors along the manometer catheter differentiates between low spatial resolution, termed conventional manometry, and HRM (Figure 1.19) (521). Conventional manometry catheters have 3-8 pressure sensors widely spaced at 3-5 cm, whereas HRM catheters have 20-36 pressure sensors spaced at intervals of 1cm or less (16). Closely spaced pressure sensors allow for more accurate interpolated data, which is representative of the contraction wave along the total length of the pharynx (12, 14, 31, 527, 528), and provides greater accuracy when recording fast skeletal muscle pressure changes of the pharynx and UOS (125). Software is used for data interpolation from digitised HRM recordings, averaging the pressure values between the sensors, providing for a continuous isobaric colour contour called a pressure topography plot (Figure 1.19)(13). Pressure topography plots are described in more detail in Section 1.5.2.1. HRM is rapidly replacing conventional (traditional) manometry (12-15), which has allowed it to become the gold standard in oesophageal motility assessment (16, 17) and has led to its growing recognition for the assessment of pharyngeal swallowing (19-23).

Figure 1-19 COMPARISON OF CONVENTIONAL (TRADITIONAL) MANOMETRY AND HIGH-RESOLUTION MANOMETRY.

On the left, a conventional manometry tracing is shown with pressure sensors recording the changes of oesophageal pressures at 5cm intervals. On the right, a topography plot represents pressure recordings that are detected by high-resolution manometry sensors spaced 1cm apart (529).

1.5.1.4 Individual Pressure Sensor Variability

Individual pressure sensor variability, commonly referred to as pressure sensor drift, is a measurement error from the original calibrated system and may occur due to pressure, temperature and/or environmental changes over time (513-515). This results in pressure measurement instability during the assessment (513, 515), diminishing the accuracy of the pressure data acquired. Thermal compensation is a technique available to reduce this error using two methods: (1) one-point correction, where the study is ceased following removal of the catheter without any external pressure resulting in subtraction of pressures immediately following extubation from those at the beginning (513); or (2) two-point correction, where the catheter is placed in 37 degree water for two minutes and lifted in the air without external pressure and the study calibrated at this time point, followed by a second time point following extubation resulting in the drift between these two time-points to interpolate (514). In an *in vitro*

study, individual pressure sensor variability was demonstrated over a five hour duration (514). However, minimal variability was observed at approximately 20 minutes, which is useful considering P-HRM-I studies are often reported to have a duration of less than 13 minutes (496). Thus, whilst it is important to understand the risks of individual sensor pressure variability causing reduced accuracy of recordings, as well as methods to minimise this occurrence, it appears this likely has minimal impact on the accuracy of the results in a standard duration P-HRM-I assessment.

1.5.1.5 Individual Pressure Sensor Variability

The effect of the catheter presence itself on swallowing is another factor that can potentially affect the accuracy of the results. Previous studies in healthy cohorts have shown the presence of a nasogastric tube (fine bore and wide bore) to be associated with an increased duration of total swallowing and UOS opening compared to no tube (516, 517). Interestingly, in patient cohorts it is contentious whether or not a nasogastric tube results in increased aspiration; some studies have reported no change in aspiration status (530-532) but others have observed an increase in aspiration status on VFSS (533, 534). Whilst the effect of the presence of the catheter affecting the pressure and impedance data should be acknowledged, it is unlikely to be a concern when patient/participant cohorts are compared to normative data collected in the same from age and gender matched controls.

1.5.1.6 Topical Anaesthesia

The administration of topical anaesthesia prior to an invasive procedure, such as P-HRM-I, aims to maximise patient comfort and reduce anxiety (535). However, there is disagreement regarding the effectiveness of topical anaesthesia in maximising patient comfort and overall procedural tolerance (518, 535-537). Additionally, topical anaesthesia applied from the nostril to the oropharyngeal and laryngeal oral mucosal surfaces is not used in some P-HRM-I protocols due to concerns that it may alter and diminish the sensory and motor aspects of oropharyngeal swallowing, which could therefore affect the reliability of the data (518, 538, 539). In one P-HRM-I study, the administration of topical anaesthesia, 0.4 mL of 2% viscous lidocaine hydrochloride, did not result in changes to participant discomfort scores but was associated with reduced pharyngeal pressures (518). However, in contrast, a recently published paper reported

comparable pharyngeal pressures with and without topical anaesthesia (540). Similar concerns have been raised in the FEES literature (441). Although reports have been conflicting, some studies have reported an association with topical anaesthesia and increased frequency of swallowing (541) and increased bolus dwell time (542). Whilst increased laryngeal penetration and/or aspiration have also been reported with topical anaesthesia (535), other studies have not found the same result (537, 543). Accordingly, the judicious application of topical anaesthesia during the P-HRM-I procedure is currently recommended by the International P-HRM_I Working Group Protocols (21). The publication of normative P-HRM-I reference data used a protocol of judicious topical anaesthesia, consistent with these international recommendations (544). Further investigation is required to establish whether the historical practice of topical anaesthesia provides significant benefit (545); as well as the true effect of its administration on swallow function (535, 537, 546).

1.5.2 Pharyngeal and UOS Lumen Occlusive Pressures and Bolus Movement Acquisition and Analysis

1.5.2.1 Pressure Topography Plots

Pressure topography plots provide visualisation of the pharyngeal swallow along the length of the pharynx represented as a colour continuum (13). Pressure topography plots enable regions of high and low pressure profiles to be localised, tracked and quantified, either across the entire pharynx or in relation to discrete anatomical regions (547). Contractility is represented as a constant (isobaric) value of the individual sensors with continuous representation across anatomical space and time (548). In Figure 1.20, a pressure topography plot, also known as Clouse plots, of an oesophageal swallow is shown. The y-axis displays the oesophageal anatomical regions; the x-axis displays time measured in seconds. The warm colours, such as red and orange, signify higher pressures and cooler colours, such as green and blue, represent lower pressures (16).

Figure 1-20 LANDSCAPE 3D IMAGE OF THE HRM PRESSURE DATA COLLECTED DURING AN OESOPHAGEAL ASSESSMENT.

The areas of higher pressure are represented by warmer colours with the darkest red representing the greatest pressures within an anatomical region across time (14).

In P-HRM-I, the pressure topography plots provide visualisation of the pharyngeal swallow with identified anatomic locations, including: the velopharynx, mesopharynx, hypopharynx and UOS (Figure 1.21). The pressures in these four anatomical regions correspond to the average of the pressures detected by the sensors in those regions (21). Additionally, qualitative assessment of the pressure topography plot is possible with identification of significantly reduced or increased pressures (497).

Figure 1-21 SIMULTANEOUS P-HRM WITH VFSS OF A SINGLE, NORMAL PHARYNGEAL SWALLOW OF A 10 ML LIQUID BOLUS.

A: P-HRM derived pressure topography plot of the single swallow; B: Individual P-HRM pressure sensors within the anatomical regions that correlate with the pressure topography plot, displayed as a line graph; C: VFSS still frame prior to pharyngeal swallowing; and D: during the pharyngeal swallow (21).

1.5.2.2 Pharyngeal and UOS Lumen Occlusive Pressures

During pharyngeal swallowing, adequate pharyngeal and UOS contraction requires both longitudinal and lumen occlusive horizontal pressures (5), which can be measured using P-HRM (549). The retrieval of the pharyngeal and UOS lumen occlusive pressure data from the respective anatomical regions is averaged within that respective region, and has been described by various groups (503, 504, 528, 550, 551). It is generally accepted that the velopharynx pressure recording is an average from 2 pressure sensors, whilst the mesopharynx, hypopharynx and UOS pressures are an average from 3 pressure sensors across each region (21). Multiple pressure sensors are necessary for detection of accurate UOS pressure measurements, given that the UOS is known to move superiorly between 2-2.8cm during swallowing and that the UOS is a high-pressure zone (150, 525). These pharyngeal and UOS lumen contractility/pressure values may be calculated as a peak pressure or as a contractile integral. A peak pressure provides information regarding the maximum pressure of that specific anatomical region (503, 552). A contractile integral pressure is calculated as the mean pressure of the anatomical region multiplied by its duration and length (or span) of the specified anatomical region, which is considered to provide a more accurate measure of pressure generation after bolus propulsion (21, 504, 553). This is particularly the case for

contractile integrals measuring the velopharynx and mesopharynx, as there are multiple points of contact between the pharyngeal structures surrounding the catheter (554). Recently, the P-HRM International Working Group recommended a standardised set of core pressure and impedance measures for application in both clinical and research settings, which are outlined in detail in *2.4 P-HRM Standard Procedure* (21).

1.5.2.3 Intraluminal Electrical Impedance

Intraluminal electrical impedance when simultaneously conducted with manometry provides insight into the relationship of movement a distending bolus (bolus flow) and pharyngeal pressure (499, 555, 556). Multichannel impedance measures allow for the differentiation of complete or partial bolus transit, stasis and anterograde or retrograde bolus movement (521, 557, 558). A limitation of this, however, is the inability to identify the volume of partial transit or stasis (12), which can be addressed with the addition of a visual instrumental assessment (494).

Solid-state HRM catheters may contain paired impedance segments (2 cm length) comprising of paired metal electrode rings separated by an isolator (499) that, along with the surrounding pharyngeal or UOS lumen, form a closed electrical current loop (12, 559). Intraluminal electrical impedance measures the changes in resistance (ohms), which is inversely proportional to the electrical conductivity of the luminal contents and the cross-sectional area (555, 556). Whilst air has a high resistance to current flow (high impedance), liquids have lower resistance (low impedance). Prior to bolus administration, the resting impedance measure is defined as the baseline electrical current conducted between the rings along the muscular wall. During bolus transit, the air volume ahead of the bolus has increased resistance, which is detected by higher impedance values. During liquid bolus entry, there is a distinct decline in impedance (below the resting impedance measure) representing reduced resistance of the liquid bolus. When the body of the bolus spans the measuring segment, this represents the minimum impedance value. As the bolus leaves the measuring segment due to luminal occlusion, a return to resting baseline measures occurs (Figure 1.22) (12, 559).

Figure 1-22 BOLUS MOVEMENT WITH CORRESPONDING INTRA-LUMINAL IMPEDANCE MANOMETRY OF AN INDIVIDUAL SEGMENT.

The F-point indicates the arrival of the bolus head, with an increase in impedance demonstrated on the graph; the b-point indicates the moment of maximum bolus volume across the paired

impedance segment resulting in the lowest impedance value; and the c-point indicates the contraction on the bolus tail causing rapid lumen occlusion and an increase in impedance (560).

Omari and colleagues are pioneers who have extensively investigated simultaneous acquisition of impedance and pressure data in P-HRM-I analysis (499, 558, 561), who have acknowledged the difficulties associated with the measurement criteria for bolus transit during the pharyngeal phase (499, 562). In the assessment of oesophageal bolus transit using impedance line tracings, bolus entry is defined as a 50% or more decrease from baseline, and clearance is defined as sustained (> 5 seconds) increase from baseline of 50% or more (563, 564). However, this criterion is not appropriate for measuring bolus transit in the pharynx due to the increased variability of baseline impedance measures associated with the short timing of the pharyngeal phase, mucosal contact of pharyngeal structures, the presence of residue and accumulative saliva (499, 562).

Over the past ten years, refinement of the criterion for the measurement of impedance during the pharyngeal swallow has occurred with several previously published versions no longer in use (154, 498, 565-567). Currently, bolus movement as measured by the nadir (lowest value) impedance at the hypopharyngeal and UOS regions is the inverse of a corresponding maximum admittance value, which corresponds to the distension pressure of these regions (Figure 1.23) (497). The maximum admittance can infer the maximum luminal opening during bolus flow (497), which may be more intuitive for clinical application.

Figure 1-23 REPRESENTATION OF PRESSURE AND ADMITTANCE (INVERSE OF IMPEDANCE) GRAPHS THROUGH THE PHARYNX AND UOS.

A: Pharyngeal pressure topography plot with the position of pressure/admittance recordings relative to the UOS apogee (highest point of the UOS); B: Six pressure/admittance graphs displaying the velopharynx, mesopharynx, hypopharynx, UOS apogee above and below the uos and proximal oesophagus; and C: UOS pressure and Admittance Plot (21).

1.5.2.4 Analysis Algorithms

Manual or automated analysis of the raw manometric and intraluminal electrical impedance data with subsequent analysis for comparison with normative referenced ranges has been described

(503, 544, 558, 568, 569). Commercially available systems manufactured by Medical Measurement Systems, Sandhill Scientific, and Sierra Scientific incorporate various software platforms that convert the manometric and impedance data to line tracings and pressure topographic maps. Distinct equipment is required for the simultaneous manometry and impedance testing compared with exclusive manometry testing (512).

Manual analysis of pressure and timing data has been acknowledged as a time-consuming process and unsuitable for clinical application (503, 504). This process involves manual placement of pressure markers from the velopharynx to the UOS, and comparison of these numbers against published normative data sets (503). Manual analysis of the impedance pattern has been reported, which involves observations of bolus transit patterns representative of effectiveness of bolus flow (558, 563). Manual analysis is limited to the assessment of maximum pressures and durations and bolus clearance, which is unable to provide a sophisticated analysis of the biomechanical events during swallowing (568).

In contrast to the manual analysis methods (503, 504), automatic methods require minimal training and have good reliability (19). Automated methods of pressure and/or impedance data extraction from the spatiotemporal plots enables analysis of a large quantity of variables and supports potential application of this technology into the clinical setting (567, 568). Whilst automated analysis is necessary to assist with clinical practice, it does not replace clinical interpretation (512), which requires further training. Currently, there are two international groups, one in Madison, USA and the other in Adelaide, Australia, that use automatic methods of data extraction and analysis software platforms via MATLAB (551, 554, 567-570). The Madison Group, McCulloch and colleagues, acquire pressure and timing data and report measures inclusive of peak pressures, pressure gradients of defined pharyngeal regions and timing onset and offset from the elevated pressure, pressure gradients and velocity (551). These methods were described in validation studies and demonstrated good inter- and intra-rater reliability (19, 568). The Adelaide Group, Omari and colleagues, acquire pressure, impedance and timing data using the software platform Automated Impedance Manometry (AIM) analysis to conduct pressure-flow analysis. In 2018, the AIM software platform was launched as an open-access program via swallowgateway.com™ to support increased accessibility for use in the clinical setting (571). These methods have been validated with VFSS (562, 567, 569, 572) and demonstrated good intra- and inter-rater reliability in both inexperienced and experienced users (571, 573, 574).

1.5.3 P-HRM with and without Impedance Measures in Healthy and Dysphagic Cohorts

There have been a large number of publications evaluating pharyngeal swallowing using P-HRM with and without impedance measures in both healthy (80, 105, 121, 154, 162, 525, 528, 544, 553, 575-579) and dysphagic (107, 563, 567, 580-586) cohorts. An understanding of the pressure and bolus movement data derived from P-HRM-I technology in healthy cohorts provides for comparison with homogenous dysphagic cohorts (22), which is key to identifying characteristic swallowing patterns. Furthermore, P-HRM with and without impedance, when utilised as an intervention outcome measure, provides quantifiable pressure and timing data that can signify intervention effectiveness (21, 587) and assist in guiding dysphagia therapy (503). Of the 33 studies that have evaluated swallowing using P-HRM with and without impedance, a range of systems for acquisitions, catheter type, protocols and use of topical anaesthesia are observed (*Refer to Appendix 1*).

1.5.3.1 P-HRM with and without Impedance Measures in Healthy Cohorts

A large number of publications have investigated the biomechanics of pharyngeal and UOS swallowing using P-HRM with and without impedance in healthy individuals (80, 105, 121, 154, 162, 525, 528, 544, 553, 575-579) with observed within-subject variability (588, 589) and between-subject variability (589, 590), demonstrated age related changes (29, 553, 583, 591-593), and sleep associated changes (594). In addition, these publications have reported modulation of the pharynx and UOS in response to bolus consistency (190) and bolus volume (85, 106, 504, 550, 595).

1.5.3.2 P-HRM with and without Impedance Measures in Dysphagic Cohorts

When compared with healthy controls, changes in pharyngeal pressure and/or impedance measures using P-HRM with and without impedance have also been reported in patients with dysphagia with a wide range of aetiologies. These include: heterogenous groups (107, 563, 567, 580-586), Motor Neurone Disease (154, 591, 596), Parkinson's Disease (26, 597, 598), Huntington's Disease (558), Stroke (599, 600), vagal paralysis (601), Head and Neck Cancer (HNC) (28, 561, 572), total laryngectomy (602-604), unilateral cleft lip and palate (605), large

cervical osteophytes (606), post-surgical intervention in OSAS (1) and a hospitalised elderly cohort (607).

1.5.3.3 P-HRM with and without Impedance Measures as an Interventional Outcome Measure

In healthy cohorts, several studies have evaluated various swallowing therapies using P-HRM with and without impedance to derive biomechanical swallowing changes that occur as a result of the therapy. These include emergent therapeutic techniques: expiratory muscle strength training (EMST) (608), neuromuscular electrical stimulation (538) and anodal transcranial direct current stimulation (609); laryngeal adductor reflex stimulation (610), capsaicin (611), the opioid drug remifentanil (612, 613) and topical anaesthesia (518). Additionally, the impact of swallowing manoeuvres and body positioning on the biomechanics of swallowing have been reported in healthy participants, including Mendelsohn and effortful swallowing (20, 173, 552, 614-616), Valsalva (617), head rotation and chin tuck (551, 618), head rotation and head tilt (619), head rotation (549), tongue-hold manoeuvre (620, 621), and body positioning (594, 622).

P-HRM with and without impedance measures have also been utilised as an interventional outcome measure in dysphagic cohorts. These include: the therapeutic effect of effortful swallow (623), the effect of cricopharyngeal peroral endoscopic myotomy of UOS dysfunction in Parkinson's disease (624), the effect of transoral robotic surgery effects for the treatment of HNC (625), the effect of sensory stimulation (cold, sour, carbonation) in a heterogenous dysphagic cohort (626), the effect of chin posture in oesophagectomy (627), a single case study on the effect of biofeedback on hypotonic UOS (628), vocal fold augmentation procedure for the management of dysphagia associated with unilateral vocal fold palsy/paresis (629), type 1 thyroplasty for the management of vocal fold immobility (630), a single case study on the effect of biofeedback therapy (631), a single case study on the effect of a lingual isometric therapeutic device (632), the effect of standard dilatation with a modified balloon dilatation in patients with brainstem stroke (633), and a single case study on the effect of cricopharyngeal myotomy for the management UOS restriction associated with Motor Neuron Disease (27).

1.5.4 Clinical Application of Pharyngeal High-Resolution Manometry with Impedance

P-HRM with or without impedance is expected to have increased uptake for the assessment of oropharyngeal swallowing by speech pathologists in the coming years (24, 32). For successful integration into clinical practice to occur, an understanding of the technology itself, the benefits that it can offer, and the appropriateness of use is critical. The integration of pressure derived data from manometry with measures of bolus movement (flow) derived from impedance and/or visual instrumental assessment provides a comprehensive swallow assessment (10, 22). In the current literature, of the 33 studies evaluating pharyngeal dysphagia using P-HRM technology, seven used P-HRM alone without bolus movement measures of impedance or VFSS (28, 598, 601, 602, 605, 607, 634). These *pressure-only* studies present with substantial limitations because omitting bolus flow measures reduces the clinical information that can be derived from a more complete swallowing assessment (22). This is emphasised in the normal physiological events of oropharyngeal swallowing (*Section 1.1*). Of the remaining 26 studies, 11 used concurrent VFSS (107, 580, 582, 584-586, 596, 597, 599, 633, 635), 13 used concurrent VFSS and impedance (1, 26, 30, 154, 558, 561, 563, 567, 572, 581, 583, 603, 606), and two used concurrent impedance (591, 600). Limited acquisition and analysis of impedance data alongside pressure data may be attributable to the changing evaluation criteria and swallowing metrics reported in the literature over past ten years (154, 498, 565-567). Since 2016, there appears to be more consistency in the reporting of impedance measures (497). Of particular relevance to this thesis, P-HRM-I measures have not been previously reported in the OSA, critically ill following extubation, and following HNC treatment cohorts.

The use of P-HRM with and without impedance as an interventional outcome measure has been reported in 11 studies; four of these reporting on single cases. Of the remaining seven studies, six have been published since 2019 (624-627, 629, 630), likely representing the increased recognition of this technology to evaluate the effectiveness of an intervention (21). Of note, these aforementioned studies were published during the data collection period of the two interventional outcome studies included in this thesis (*Chapters 6 and 9*). Nil prospective studies utilising the interventions evaluated in this thesis have been previously reported.

2. AIMS

The overall aim of this research program was to advance the understanding of the swallowing biomechanics that exist in different clinical dysphagia cohorts, using P-HRM-I measures. Unlike other swallowing assessment methods, P-HRM-I can identify and localise alterations in pressure and bolus flow during swallowing to determine the underlying pathophysiological breakdown leading to dysphagia, which provides considerable opportunity for clinical translation. Accordingly, the specific aims of this thesis were to:

1. Determine the P-HRM-I measures and patterns that may distinguish and characterise dysphagia in homogenous adult cohorts with different medical aetiologies when compared to healthy controls.
2. Explore the utility of P-HRM-I as an interventional outcome measure and identify biomechanical changes following the intervention to determine the effect on the swallowing mechanism.

This chapter outlines the research aims, questions, hypotheses, rationale and significance for each of the six observational studies conducted in this thesis.

2.1 Homogenous Cohort Observational Studies

2.1.1 Dysphagia Assessment in OSA (Chapter 4)

2.1.1.1 Aims

1. To analyse and describe the pharyngeal swallowing biomechanics and dysphagia symptoms in participants with moderate-severe OSA.

2.1.1.2 Research Question

1. What P-HRM-I measures are altered in participants with OSA when compared with healthy controls?

2.1.1.3 Hypothesis

1. Pressure and impedance measures representative of sensory impairment in participants with moderate-severe OSA will be altered when compared to healthy controls.

2.1.1.4 Rationale and Significance

Alterations in swallowing associated with OSA are becoming more widely recognised, however the mechanisms that contribute to altered swallowing have not yet been established (247, 276). Neural injury associated with OSA causing sensory impairment and peripheral disturbances in swallowing has been hypothesised (272, 274, 277-279). However, studies investigating the swallowing biomechanics in people with OSA using P-HRM-I are lacking. Identification of the altered swallowing biomechanical measures in participants with OSA may identify the contributing mechanisms to the pathophysiology of dysphagia in this population.

2.1.2 Dysphagia Assessment Post OSA Surgery (Chapter 5)

2.1.2.1 Aims

1. To use P-HRM-I to assess the swallowing biomechanics of participants following mUPPP+/-CCT surgery for OSA and compare these results to healthy controls.

2.1.2.2 Research Question

1. What P-HRM-I measures are altered in people who have had mUPPP+/-CCT surgery for the management of OSA when compared with healthy controls?

2.1.2.3 Hypothesis

1. The mUPPP procedure will result in reduced velopharyngeal contractile pressures compared to healthy controls.
2. CCT procedure will result in reduced mesopharyngeal contractile pressures compared to healthy controls.
3. Altered UOS modulation will be identified following mUPPP+/-CCT surgery when compared to healthy controls.

2.1.2.4 Rationale and Significance

Dysphagia has historically been reported following OSA surgery (248, 636), however these reports commonly used VFSS assessment following historical surgical techniques including complete uvula and excessive velar tissue resection (294, 295, 313, 636). Consequently, it was unknown whether previous publications accurately represented swallowing function following contemporary surgical procedures for OSA, such as mUPPP+/-CCT. Our group previously investigated swallowing post mUPPP+CCT using P-HRM-I technology and identified post-operative altered UOS function suggesting altered sensory modulation (1). However, this was a pilot study in a small cohort (n=12) with wide ranging time points following surgery. The application of P-HRM-I to characterise biomechanical swallow changes in a larger cohort of post-surgical patients when compared with healthy controls aims to provide further understanding of the impact of surgery on swallow function and potentially assist clinicians in identifying those patients who may be at an increased risk of post-operative dysphagia.

2.1.3 Dysphagia Assessment in the Critically Ill Following Extubation or decannulation (Chapter 7)

2.1.3.1 Aims

1. To utilise P-HRM-I to evaluate the pharyngeal biomechanics to objectively characterise swallowing in critically ill participants following extubation or decannulation and determine the effect of endotracheal intubation duration on swallowing.

2.1.3.2 Research Question

1. What P-HRM-I measures are different in the critically ill following extubation or decannulation when compared with healthy controls?
2. Is prolonged endotracheal intubation a risk factor for dysphagia?

2.1.3.3 Hypothesis

1. P-HRM-I measures will be significantly different in the critically ill participants following extubation or decannulation when compared to age-matched healthy controls.
2. Prolonged intubation will be associated with dysphagia.

2.1.3.4 Rationale and Significance

Dysphagia is common in critically ill patients following extubation or decannulation (251, 318) and can have considerable impact on health outcomes, such as poor quality of life and increased morbidity and mortality risk (251, 319-322), as well as on health care utilisation and cost (321, 322, 324-327). Although post extubation dysphagia remains inadequately identified (251, 637, 638), clinical risk factors have been reported in the literature, including increased duration of endotracheal intubation (319, 323, 348). Aspiration is the most frequently reported primary outcome measure (346), however the mechanisms that result in aspiration or altered swallowing function at the time of extubation and/or decannulation are seldom studied or discussed (349). This may be due in part to VFSS assessment being difficult to conduct in this setting. P-HRM-I, on the other hand, can be conducted at the bedside and this study aims to quantify swallowing outcomes in this participant cohort to reveal novel swallowing mechanisms that contribute to dysphagia and determine whether prolonged intubation is a risk factor for mechanistic alterations in swallowing.

2.1.4 Dysphagia Assessment post-HNC treatment (Chapter 8)

2.1.4.1 Aims

1. To use P-HRM-I to assess the swallowing biomechanics in participants with HNC who undergo multi-modality treatment and correlate these metrics with VFSS measures.

2.1.4.2 Research Question

1. What pressure and impedance derived measures are altered in the post-HNC treatment cohort when compared to healthy controls?
2. What VFSS measures of aspiration and residue are significantly correlated with pressure and impedance derived measures?

2.1.4.3 Hypothesis

1. UOS opening and relaxation (UES Max, UES IRP) and hypopharyngeal intra-bolus pressure, as an indirect measure of UOS function, will be impaired and pharyngeal contractile pressures (PhCI, VCI, MCI and/or HPCI) will be reduced compared with healthy controls.
2. Pharyngeal residue will be associated with reduced mesopharyngeal contractile pressures (MCI).

2.1.4.4 Rationale and Significance

Multi-modality treatment for HNC can result in acute and long-term dysphagia, which is negatively associated with health-related quality of life (378). VFSS has been primarily used to recognise pathophysiological oropharyngeal swallowing changes following HNC treatment. Abnormalities of the swallow mechanism identified with VFSS have included base of tongue dysfunction, reduced pharyngeal contraction, and reduced UOS opening (366, 380-388). Altered bolus flow outcomes of residue and aspiration have also been identified in VFSS and FEES studies following HNC treatment. Current P-HRM-I studies have not completely characterised swallow function following HNC treatment. Thus, further evaluation of the altered swallowing biomechanical measures may identify contributing mechanisms to the pathophysiology of dysphagia in this population. Additionally, comparing the biomechanical findings with VFSS observations may provide greater understanding of the swallowing alterations following HNC treatment.

2.2 Pre- and Post- Intervention Studies

2.2.1 Dysphagia Assessment Pre- and Post-OSA surgery (Chapter 6)

2.2.1.1Aims

1. To compare swallowing outcomes in participants diagnosed with OSA prior to- and following- mUPPP+CCT surgery.

2.2.1.2 Research Question

1. What P-HRM-I measures are altered in people who have had mUPPP+CCT surgery for the management of OSA post-surgery when compared with pre-surgical baseline?

2.2.1.3 Hypothesis

1. mUPPP procedure will result in a reduction of velopharyngeal contractile pressures.
2. CCT procedure will result in a reduction of the mesopharyngeal contractile pressures.

2.2.1.4 Rationale and Significance

Dysphagia has been reported following the surgical management for OSA. However, alterations in swallowing have also been identified in people with OSA who have not yet undergone surgical intervention. Thus, the degree of swallowing changes that may be attributed to upper airway surgery for OSA management compared with the pathogenesis of OSA itself, remains unknown. The prospective evaluation of swallowing pre- and post-upper airway surgical intervention for the management of OSA has been conducted in two studies (290, 314). However, these studies used visual instrumental swallowing assessments and did not report on outcomes following the mUPPP+CCT surgical technique. Although both studies evaluated different swallowing outcomes across different surgical techniques, no significant VFSS-derived swallowing changes were reported following surgery. To date, no studies have utilised P-HRM-I to compare post-mUPPP+CCT swallowing biomechanics to pre-surgical baseline in people with OSA. The application of P-HRM-I may reveal biomechanical alterations that have not previously been detected by other swallowing assessment techniques and to provide further understanding of the impact of this contemporary surgery on swallowing.

2.2.2 Dysphagia Assessment Pre- and Post-Tongue Base Augmentation (Chapter 9)

2.2.2.1 Aims

1. To evaluate the effect of tongue base augmentation in participants with dysphagia following HNC treatment on swallowing outcomes using P-HRM-I biomechanical data, videofluoroscopy swallowing study (VFSS), and self-reported symptoms of dysphagia.

2.2.2.2 Research Question

1. What P-HRM-I measures are altered in people who have had a tongue base augmentation procedure for the management of moderate-severe dysphagia following HNC treatment when compared with baseline?

2.2.2.3 Hypotheses

1. Following tongue base augmentation, increased mesopharyngeal wall volume/thickness, measured using magnetic resonance imaging (MRI), and improved mesopharyngeal force generation, measured by P-HRM-I, will be observed.
2. Following tongue base augmentation, reduced post-swallow pharyngeal residue and improved patient-reported dysphagia symptoms will occur.

2.2.2.4 Rationale and Significance

Dysphagia following HNC treatment has been identified as a strong predictor of reduced health-related quality of life (378, 639, 640). Changes in eating habits occur in up to 40% of people following HNC treatment (641), while 3-10% of patients require percutaneous endoscopic gastrostomy (PEG) for nutritional support at 12 months or more after treatment (642, 643). Accordingly, there has been considerable research targeting improvements in swallowing outcomes following HNC treatment. The initiation of swallowing exercises prior to, during, and following treatment was one strategy aimed at maximising swallowing muscle strength and range of movement (644). However, the efficacy of swallowing exercises is unclear, with inconsistent treatment effects being demonstrated (645). Tongue base dysfunction is recognised as a contributory mechanism of dysphagia following HNC treatment as measured by VFSS. In particular, reduced tongue base and pharyngeal wall muscle volume has been

associated with reduced pharyngeal constriction and increased pharyngeal residue (646). Augmentation of the tongue base aims to target the key anatomical sites that contribute to tongue base dysfunction (380, 647) and has been reported to result in improved swallowing outcomes (648, 649). It has been hypothesized that this procedure artificially augments the mesopharyngeal volume and, as a biomechanical consequence, increases the force generation capacity during swallowing. However, evaluation of swallowing biomechanics before and after the procedure has not occurred. The application of P-HRM-I aims to provide further understanding of the impact of this novel surgery on swallowing and assist clinicians in identifying those patients who may benefit the most from the procedure methodology.

3. METHODOLOGY

3.1 Ethical Approval

Ethical and governance approval was granted by the Southern Adelaide Clinical Human Research Ethics Committee for the studies presented in this thesis, which were all candidate-driven. All participants provided written informed consent.

The approval numbers assigned by the Office for Research and the titles are:

(1) 156.18, The investigation of dysphagia following oropharyngeal surgery for obstructive sleep apnoea;

(2) 283.11, Assessment of swallowing function and aspiration risk in adult patients with dysphagia;

(3) 39.17, Pharyngeal augmentation for dysphagia therapy: A novel surgical approach for dysphagia management; and

(4) 202.15, Incidence of post extubation dysphagia in short-term and long-term stay critical care patients using high-resolution pharyngo-oesophageal manometry and impedance.

3.2 Swallowing Outcome Measures

The study protocols comprised of the collection of a number of swallowing outcome measures, including PROMs of swallowing, P-HRM-I and/or VFSS. The broad methodology of the conducted studies is described in the following section, with specific amendments required for each of the cohort and intervention studies, which are outlined in their respective chapters.

3.2.1 Patient Reported Outcome Measures of Swallowing

PROMs of swallowing were collected in the homogenous cohort studies to determine self-reported symptom severity, and in the intervention studies to evaluate perceived treatment effectiveness (399). The Sydney Swallowing Questionnaire (SSQ) is a validated 17-item questionnaire that is considered to be a high-quality self-reported measure of swallowing (399) to assess symptomatic oropharyngeal dysphagia (650, 651). Sixteen of the seventeen questions in the SSQ are presented as a 100 mm length visual analogue scale. One question (Q 12) has a question score from 0-5 to describe time taken to complete a meal, which is then multiplied by 20 to enable conversion along the 0-100 scale, providing consistency with the other 16 questions (651). The SSQ was validated in a heterogenous neurogenic population (n=48) diagnosed with Zenker's diverticulum (651). Normative total SSQ scores in a non-dysphagic adult cohort (n=73) have been published (650); the mean total SSQ score was 72.3 (SD = 56.7; 95 % CI [59.8, 84.9]) with an upper limit of normal determined at 234 (with a 90 % CI [193, 277]). Interestingly, no gender or age affect was observed (650), particularly as gender (544) and age (591) are recognised factors to influence swallowing.

Functional Swallowing Outcome

The Functional Oral Intake Scale (FOIS) is a validated clinician-rated swallowing outcome measure to categorise food and fluid intake levels (652). The FOIS is a seven-item scale comprising of levels 1-3 defining alternative nutritional requirements and levels 4-7 defining food and fluid status without alternative nutritional support. In the original validation study, the FOIS demonstrated high-reliability and sensitivity of changes in oral intakes status in a stroke population (652).

3.2.2 Videofluoroscopic Swallow Study

VFSS was conducted to identify abnormal bolus flow outcomes of penetration, aspiration and residue. It was simultaneously collected with P-HRM-I in a sub-set of participants in the OSA cohort (*Chapter 4*), in all of the participants in the post-HNC treatment cohort (*Chapter 8*) and in the pre- and post- tongue base augmentation intervention study (*Chapter 9*). Each VFSS was conducted in the Radiology suite at Flinders Medical Centre, Adelaide, Australia using a videofluoroscope (Artis zee multi-purpose, Seimens Healthineers) and recorded at 15 frames per second in-line with Radiology department procedures. It is acknowledged that a reduced frame rate of 15, when compared with 30, may result in limited interpretation of some impairments (475, 478).

3.2.2.1 Standard Procedure

The standard VFSS protocol consisted of a total of eight swallows, which included a 5,10 and 20 mL volume of thin and extremely thick fluids observed in the lateral plane. Repeat 20 mL volumes of thin and extremely thick fluids was observed in the anterior-posterior plane. The bolus was prepared using standardised P-HRM-I bolus medium (SBMkit™, Trisco Foods Pty Ltd, Brisbane, Australia)(544) with 100 mL of liquid barium (Polybar barium sulphate suspension; Bracco Diagnostics Inc, Monroe Township, NJ, USA) used with tap water to provide opacity of the tested boluses during testing. Bolus preparation, including differing viscosities, is described in further detail in Section 3.4.3.1 below. This standardised bolus set was used for all the P-HRM-I and/or VFSS swallow assessments apart from the critically ill cohort study (*Chapter 6*). Whilst a standard protocol was followed, the bolus preparation for this study was reflective of the procedures at the time. The thin liquid bolus comprised of 0.9% saline and the extremely thick bolus was the commercial standardized product of EFT Viscous Bolus (Sandhill Scientific, Denver USA).

3.2.2.2 VFSS Measures

Premature spillage was defined as entry of the bolus into the pharynx without the initiation of a swallow, which is typically associated with poor oral containment (45). Penetration and aspiration was evaluated using the validated 8-point penetration-aspiration scale (PAS), which was originally developed for use in VFSS (455) and has been subsequently adapted for use in FEES (653). Now widely used across both clinical and research settings, the PAS quantifies the observed anatomical level of airway invasion of material, whether an airway clearance response is initiated, and the effectiveness of the response (455). A PAS > 2 is considered indicative of abnormal swallowing (94, 654). A PAS value between 2-5 represents penetration and a PAS value between 6-8 represents aspiration (455). Vallecular and pyriform sinus residue were quantified using the normalised residue ratio scale (NRRS)(483) via the open-source image analysis software (Image J, National Institute of Health, Rockville, MD, USA). The ratio of post-swallow residue relative to the outlined valleculae (NRRSv) or pyriform sinus (NRRSp) regions was captured. Abnormal post-swallow residue is defined as a NRRS > 0.1 (94).

In addition to these validated quantification assessment tools, the Dynamic Imaging Grade of Swallowing Toxicity (DIGEST) (482) was utilised in the post-HNC treatment cohort (Chapter 8) and in the pre- and post-tongue base augmentation procedure cohort (Chapter 9). The DIGEST was intended for interpretation of both swallowing safety and efficiency using VFSS in post-treatment HNC cohorts (482). This tool has a high reliability and allows for quantification of pharyngeal dysphagia severity, from mild to life-threatening according to observed integrated bolus outcomes of Safety and Efficiency. This is determined on a matrix table that includes a Safety grade, based on the maximum penetration and aspiration scale score; and an Efficiency grade, based on maximum percentage of pharyngeal residue (482). The interaction of the Safety and Efficiency grades determines the overall Summary DIGEST grade.

3.2.3 Pharyngeal High-Resolution Pharyngeal Manometry with Impedance

The fundamental outcome measures relating to pharyngeal swallowing biomechanics was assessed using the P-HRM-I technology, which was conducted across the four homogenous cohorts and two intervention studies in this thesis. Whilst the simultaneous VFSS and P-HRM-I studies were performed in the fluoroscopy suite at Flinders Medical Centre, the P-HRM-I-only studies were conducted in a clinical motility laboratory on level 3 in the Department of Gastroenterology and Hepatology at Flinders Medical Centre. The following section outlines the

standard P-HRM-I protocol; specific details relevant to each of the individual studies are described in their respective Chapters. The following section will also review the P-HRM-I Core and Additional Metrics. At commencement of candidature, the reporting of P-HRM-I with or without impedance metrics was inconsistent. This was recognised and addressed in 2019 by the P-HRM-I International Working Group, comprising of speech pathologists, gastroenterologists, otolaryngologists and scientists from twenty institutions who formulated consensus-generated P-HRM-I Core and Additional Metrics (21). These minimum set standards of measures and protocols were generated to facilitate translation of the P-HRM-I with and without impedance technology to clinical application (21).

3.2.3.1 Standard Procedure

An 8 French catheter with 32 pressure sensors (unidirectional) and 16 impedance transducers (Unisensor AG catheter, Atticon, Switzerland) was used for recording pressure and impedance data. Pressure and impedance data were acquired at 20 samples per second using the Solar GI acquisition unit (Medical Measurement System, Enschede, The Netherlands). Following a four-hour fasting period, atomised lignocaine (5%; 2-3 sprays, equivalent to 0.3 ml) was topically administered to the nasal passage and lubricant gel (2% lidocaine) was applied on the catheter to aid catheter intubation and maximise participant comfort (21, 535). Prior to trans-nasal catheter insertion, thermal compensation correction was utilised in all studies to reduce measurement error. This consisted of the catheter being placed in 37^{o}C water in a sterilised 10-inch diameter bowl, where the pressure sensors were “zeroed”; this was repeated prior to intubation without any external pressure. Insertion of the P-HRM-I catheter, known as intubation, occurred via the anaesthetised nare to approximately 15 cm; when resistance was observed it was presumed that the catheter was within the velar region. The participant was asked to position their head in a chin down position with the catheter further advanced to span the pharynx. Sips of liquids with a straw were then performed to aid catheter placement through the pharynx below the tonic UOS, which is approximately 35-40cm (497). Liquid administration via syringe was offered to participants unable to drink via a straw. Once the catheter was positioned spanning from the velopharynx to the proximal oesophagus, confirmed through observation of the pressure topography plot, the participant returned to a head-neutral position and the catheter was taped to the nose to minimise movement of the positioned catheter (Figure 3.1). A minimum 5-minute accommodation period followed (21), which allowed for subsidence of

the anaesthetic effects from the lidocaine administration and participant accommodation to the catheter.

Figure 3-1 PARTICIPANT IN AN UPRIGHT AND HEAD NEUTRAL POSITION WITH P-HRM-I CATHETER IN-SITU (8 FR, UNIDIRECTIONAL), TAPED TO THE NOSE.

Data acquisition and computer screen shown with pharyngeal and oesophageal pressure recordings visible on the display.

Bolus preparation involved the use of a standard bolus medium (SBMkit™, Trisco Foods Pty Ltd, Brisbane, Australia) of an apple flavoured saline solution (0.9% sodium chloride NaCl) mixed with 100 mL of tap water at room temperature (544). This allows for stable conductivity measures of pressure and impedance. Viscosity was tested to ensure conformance with the International Dysphagia Diet Standardization Initiative (IDDSI)(655). Thin liquids and extremely thick liquids were consistent with IDDSI 0 and IDDSI 4, respectively. A modified bolus liquid viscosity was producible using the xanthan gum based thickening agent Precise Thick-N INSTANT from the SBMkit™, with the relevant consistency levels in-line with the IDDSI framework (21). Viscosity of extremely thick liquids (consistent with IDDSI level 4) was tested using the spoon tilt test. The spoon tilt test assesses for adhesiveness and cohesion of the substance, which is defined as maintaining shape on the spoon and able to drop from the spoon with gentle movement with only a thin film remaining on the surface of the spoon (656).

Participants were studied in an upright seated posture with a head neutral position consistent with the recommended P-HRM/P-HRM-I protocol guidelines (21). The standardised protocol included testing a total of 18 boluses of 5, 10 and 20 mL volumes of thin (IDDSI 1) and extremely thick (IDDSI 4) liquids. A minimum of three repeat swallows of each liquid volume and viscosity is recommended for acquisition of valid data (Omari et al, 2019). Participants were

asked to “swallow when ready” as the syringe was placed in the mouth. When combined with VFSS, termed videomanometry, a combined protocol was developed by the group to maximise capture across volume and viscosity range whilst minimising radiation exposure (Figure 3.2).

Videomanometry Swallow Protocol

	Left Lateral	A-P (Oesoph Screen)	Without x-ray	Comments
5ml (tsp) thin IDDSI 0	*		**	
10ml (< tbsp) thin (if suitable) **IDDSI 0**	*		**	
20ml (>tbsp) thin (if suitable) **IDDSI 0**	*	*		
5ml (tsp) ex thick/puree IDDSI 4	*		**	
10ml (< tbsp) ex thick/puree (if suitable) **IDDSI 4**	*		**	
20ml (>tbsp) ex thick/puree (if suitable) **IDDSI 4**	*	*		
Solid food texture				

Figure 3-2 VIDEOMANOMETRY PROTOCOL DEVELOPED FOR THE STUDIES IN THIS THESIS.

As represented on the online data collection table, the standardised protocol comprised of triplicate 5, 10 and 20 mL thin and extremely thick fluids (IDDSI 1 and 4, respectively). VFSS Image capture order: Left lateral and Anterior-Posterior. If aspiration was observed, testing was ceased with that volume/consistency.

3.2.3.2 Sterilisation

A standardised sterilising system was used for the P-HRM/P-HRM-I catheters, which was consistent with the Flinders Medical Centre Department of Gastroenterology and Hepatology clinical guidelines. The Trio Wipe System (Tristel Pty Ltd, Victoria, Australia) is a triplicate decontamination system for non-luminated medical devices, with reported efficacy (657). The Tristel Trio Wipe System is TGA (Therapeutic Goods Administration) approved as a Class IIb Medical Device in line with AS/NZS-4187.

3.2.3.3 P-HRM-I Analysis and Measures

The P-HRM-I recordings were analysed by myself and reviewed by experts in P-HRM-I analysis (supervisor Professor Taher Omari; colleague Dr Charles Cock) to ensure validity of analysis. The analysis was conducted using the web-based platform Swallow Gateway™ (*swallowgateweway.com*, version 2020; Flinders University, Adelaide Australia). Each P-HRM-I study was exported from the Medical Measurement System (MMS) software in ASCII file (.asc) format containing de-identified information and uploaded for analysis. Individual swallows were selected by drawing a *region of interest (ROI)* spanning from the velopharynx to the oesophageal transition zone (inferior border of the proximal oesophagus). For each selected swallow, anatomical markers were placed at the velopharyngeal proximal margin, hypopharyngeal proximal margin, upper oesophageal sphincter (UOS) apogee and UOS distal margin, as well as timing markers of UOS relaxation and closure (Figure 3.3). For an additional graphical representation of the P-HRM-I Core Metrics (*Appendix 2)*.

Figure 3-3P-HRM-I RESULTS OF A SINGLE OROPHARYNGEAL SWALLOW IN A HEALTHY CONTROL.

A: A pressure topography plot displays the P-HRM-I Core Metrics, including the pharyngeal (PhCI), velo- meso- and hypo-pharyngeal contractile integrals (VCI, MCI and HPCI, respectively), which represent the contractile pressures of the pharyngeal region represented by the solid black line; the intra-bolus pressure (IBP), represented by the solid pink line; the UOS region, including the pressure metrics before (UES baseline pressure; UESBP) and during (UES integrated relaxation pressure, UESIRP) relaxation and following contraction (UES peak pressure). B: The pharyngeal contractile pressures (black line) and impedance/admittance curves (pink line). The yellow vertical lines represent the UOS relaxation and contraction. The duration (seconds) of bolus presence time (BPT) is shown by its respective blue dotted line, indicating time from the bolus in the pharynx across the duration of UES relaxation. The Distension-contraction latency (DCL) is shown by its respective blue dotted line, representing the duration from the peak of intra-bolus pressure (IBP) to the peak of the pharyngeal contraction following UOS contraction. C: The UOS pressures (black line) and impedance/admittance curves (pink line) prior to and during relaxation. The duration of UES relaxation (UES RT) is shown in blue. Abbreviated pressure flow measures are incorporated in the figure to correspond with the definitions in Table 1 below (544).

Following analysis of the individual swallows, the P-HRM-I Core and Additional Metrics were generated by the AIM software via the www.swallogateway.com platform. This automated approach to analysis provides the mean for each of the metrics. Table 3.1 defines and describes each of these metrics in further detail.

Table 3-1 P-HRM-I WITH IMPEDANCE CORE AND ADDITIONAL METRICS (21).

PHRM-i Core Metrics	
Measurement	**Definition**
Pharyngeal lumen occlusive pressure	
Pharyngeal contractile integral ***PhCI***	An integral pressure measure of pharyngeal contractile vigor spanning from the velopharynx to the upper margin of the UES (mmHg.cm.s).
Velopharyngeal contractile integral ***VCI***	An integral pressure measure of pharyngeal contractile vigor spanning the velopharyngeal region only (mmHg.cm.s).
Mesopharyngeal contractile integral ***MCI***	An integral pressure measure of pharyngeal contractile vigor spanning the mesopharyngeal region only (mmHg.cm.s).
Hypopharyngeal contractile integral ***HPCI***	An integral pressure measure of pharyngeal contractile vigor spanning the hypopharyngeal region only (mmHg.cm.s).
Hypopharyngeal intra-bolus distension pressure	
Hypopharyngeal intra-bolus distension pressure ***IBP***	The pressure 1 cm superior to the UES apogee position at the time of maximum hypopharyngeal distension (indicated by impedance/admittance) (mmHg).
UES relaxation & opening	
UES integrated relaxation pressure ***UES IRP***	A pressure measure of the extent of UES relaxation pressure, generated as the median of the lowest pressure in a non-consecutive 0.20–0.25 second window (mmHg).
UES relaxation time ***UES RT***	A measure of the duration of UES relaxation – a pressure interval below 50% of baseline or 35 mmHg, whichever is lower, in units of seconds (s).
UES maximum admittance ***UES Max Ad***	A measure of extent of UES opening. The highest admittance value (inverse of impedance) recorded during trans- sphincteric bolus flow, in units of millisiemens (mS).
P-HRM-I Additional Metrics	
Global Swallow Function	
Swallow Risk Index ***SRI***	A composite score based on a mathematical formula comprising of four hypopharyngeal swallow metrics (IBP, BPT, DCL, peak pharyngeal pressure) and provides a numerical value distinguishing normal from abnormal swallow function (SRI >15, indicates abnormal function with an increased likelihood for aspiration events).

Timing Measures	
Bolus presence time ***BPT***	Duration of the bolus in the hypopharynx prior to UES relaxation – a correlate of the dwell time of the bolus in the pharynx (s).
Distension-contraction latency ***DCL***	A timing measure from maximum pharyngeal bolus distension to the pharyngeal luminal occlusive contraction – a correlate of bolus propulsion ahead of the pharyngeal stripping wave (s).
UES pre- and post-swallow and proximal esophageal measures	
UES basal pressure ***UES BP***	The peak pressure at the level of the UES pre swallow (mmHg).
UES contractile integral ***UES CI***	An integral pressure measure of UES contractile vigor, post swallow (mmHg.cm.s).
UES peak pressure **UES PP**	The peak pressure measure at the level of the UES, measured immediately post pharyngeal contraction (mmHg).
Proximal esophageal contractile integral ***Prox Es CI***	An integral pressure measure of proximal esophageal contractility (mmHg.cm.s).

From all the P-HRM-I Core and Additional Metrics shown in Table 3.1, the Swallow Risk Index (SRI) is the only global measure of oropharyngeal swallow function. The SRI is a validated measure, which is determined from a mathematical formula derived from the integration of pressure and impedance measures. An SRI > 15 is able to identify disordered oropharyngeal swallowing and associated aspiration risk correlated with timing, weakness and obstruction aetiologies (567). Figure 3.4 displays the four pressure and impedance metrics that contribute to the derivation of the SRI, which has been strongly related to observed penetration and/or aspiration on VFSS (567). The SRI has also been investigated as a potential marker of pharyngeal residue; an SRI value of 9 or was found to be indicative of pharyngeal residue with moderate-high predictability (569).

Figure 3-4 THE SWALLOW RISK INDEX (SRI).

The SRI is derived from pressure and impedance measures of the maximum pharyngeal contractile pressure (Peak P), Intra-Bolus Pressure (IBP), duration of the bolus presence in the pharynx (BPT) and Distension-Contraction Latency (DCL) from the maximum admittance to the

maximum peak pharyngeal pressure. SRI formula: SRI = IBP x BPT/ (DLC+1) x Peak P) x 100. An SRI over 15 is considered to identify dysphagia and associated aspiration risk (497).

3.2.3.4 Controls Database

In all four of the cohort studies in this thesis, participant results were compared with data from a healthy control group. Data for the control group were sourced from a database of healthy controls (n=50) with a mean age of 46 years, age range 19-79 years; 29 females, 21 males, which has been published (544). Inclusion criteria for the control group included: adults (>18 years). Exclusion criteria: previous upper airway or gastrointestinal surgery, self-reported swallowing difficulties, gastroesophageal reflux disease, allergy to local anaesthesia, pregnancy, uncontrolled diabetes or blood pressure and medications affecting gastrointestinal motility, and medical history consistent with OSA. Healthy participants were recruited from the general community through public advertisement and had a P-HRM-I swallow assessment using the protocols as described above.

3.3 Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics Version 25.0 (*Chapters 4, 5 and 7*) and Version 26.0 (*Chapters 6, 8 and 9*) (Statistical Package for the Social Sciences; IBM Corp, Armonk, NY, USA). The average of each swallow function metric was determined per participant across each volume and consistency condition (3-5 swallows for each bolus condition). General linear mixed model analysis was performed with bolus volume and consistency as repeated measures and group as fixed factors. Bonferroni adjustment was applied to multiple pairwise comparisons. Nonparametric data were normalised by log transformation or compared using Mann Whitney U Test or Wilcoxon Test. Data are presented as means (95% CI) or median [IQR] as appropriate. A statistically significant difference between patients and controls was defined with p values <0.05.

In the following Chapters in this thesis, the novel P-HRM-I swallowing data is presented in four cohort studies that compare swallow outcomes to healthy controls and two pre- and post-interventional treatment cohort studies. The biomechanical metrics are evaluated to identify patterns of mechanistic alterations in swallowing function that assists with characterising swallowing in these different participant cohorts, as well as evaluating the efficacy of interventional techniques on swallowing function. For each study the findings are discussed in relation to the currently available dysphagia literature.

4. DYSPHAGIA ASSESSMENT IN PARTICIPANTS WITH OSA[1]

4.1 Introduction

OSA is a chronic sleep-related upper respiratory condition that is currently thought to be caused by multiple contributing mechanisms (266, 267). Dysphagia is a common but under-recognised comorbidity associated with OSA, with a prevalence ranging between 16-78% (247, 274-276). Subclinical bolus flow abnormalities have been identified in patients with OSA using visual instrumental assessment (274-276), with common swallowing impairments including premature spillage and/or delayed swallow initiation, penetration and pharyngeal residue (247). Refer to *Section 1.3.1 Epidemiology of dysphagia in OSA* for further details. Although the mechanisms contributing to dysphagia in patients with OSA are not well established (247, 276), neural injury associated with OSA causing sensory impairment and peripheral disturbances in pharyngeal swallowing have been hypothesised (272, 274, 277-279). Observations consistent with oropharyngeal sensory alterations and impaired swallowing modulation have been reported in patients with OSA, such as prolonged latency of swallowing initiation (279) and shorter duration of inspiration following swallowing (278, 279). Neuromuscular injuries, such as lower axon density within the nerve fascicles of the soft palate, have also been associated with the degree of swallowing dysfunction in patients with OSA (272).

Despite the increasing recognition of dysphagia as a complication associated with OSA, there are no known published studies that have utilised P-HRM-I to investigate the swallowing biomechanics in patients with OSA. Identification of the altered swallowing biomechanical measures could provide further insight into the underlying mechanisms contributing to the pathophysiology of dysphagia in this population.

Aim: To analyse and describe the pharyngeal swallowing biomechanics and dysphagia symptoms in participants with moderate-severe OSA.

[1] The data presented in this Chapter was **published**: Schar, MS., Omari, TI., Woods, CW., Ferris, L., Doeltgen, S., Lushington, K., Kontos, A., Athanasiadis, T., Cock, C., Chai Coetzer, C-L., Eckert, D.J., & Ooi, E.H. (2021). Altered swallowing biomechanics in people with moderate-severe obstructive sleep apnea. *Journal of Clinical Sleep Medicine, 17* (9) https://doi.org/10.5664/jcsm.9286 (*Appendix 3*). It was also accepted for **oral presentations** at the European Society of Swallowing Disorders Virtual Conference in September 2020 and the South Australian Allied Health Research Virtual Forum in October 2021. **Funding** of this study was supported by a research grant awarded by the South Australia Health/University of South Australia Allied Health Research Collaboration Grant, 2018. ($35, 000, CI M.Schar).

4.2 Methods

Participants

Ethical approval was granted by the Southern Adelaide Clinical Human Research Ethics Committee (No. 283.11 and 156.18). Participants were prospectively enrolled between November 2017- September 2020. Participants with moderate-severe OSA were recruited following referral to the Otolaryngology Head and Neck Surgery Unit at Flinders Medical Centre for suitability of upper airway surgery. Inclusion criteria: moderate-severe OSA (AHI ≥15 events/h sleep)(658) based on an overnight polysomnography sleep study, adult (≥18 years) and noncompliance with medical management of OSA. Exclusion criteria: previous upper airway or gastrointestinal surgery, self-reported laryngopharyngeal reflux/gastroesophageal reflux disease symptoms, allergy to local anaesthesia, pregnancy, uncontrolled diabetes or blood pressure, or a neurological diagnosis. Age- and gender-matched control data were acquired from an existing laboratory database (544). Refer to *Section 3.4.3.4, Methodology* for details of the healthy control data.

OSA Severity

The apnoea-hypopnoea index (AHI) measures the severity of sleep apnoea. It is the average of the apnoea (completion breathing cessation) and hypopnoea (partial breathing cessation) events per hour of sleep)(658). The AHI severity scale, includes: normal (<5); mild (≥ 5- <15); moderate (≥15 - ≥30); and severe (≥30)(658).

PROMs

All participants completed the SSQ to assess for patient-reported symptomatic dysphagia. All participants completed the Epworth Sleepiness Scale (ESS), a validated self-administered questionnaire, to assess daytime sleepiness with sleepiness defined as a score ≥ 9 (659).

Swallow Assessment

P-HRM-I and VFSS assessments were conducted and analysed according to the respective protocols described in *Section 3.4.3 and 3.4.2*, respectively.

Statistical Analysis

PROM scores and P-HRM-I metrics from the moderate-severe OSA group were compared to healthy Control group data. Refer to *Section 3.5* for details of the statistical analysis.

4.3 Results

Demographics

Demographics of the study participants are presented in Table 4.1. In the OSA group, twenty participants were enrolled, however one participant was excluded due to mild OSA (AHI <15 events/h sleep), providing a total of 19 participants for analysis. 80% (16/19) had severe OSA (AHI >30 events/h sleep) and 15% (3/19) had moderately severe OSA (AHI between 15-30 events/h sleep). Excessive daytime sleepiness was reported in 35% (7/19) of participants in the OSA group. Data for 19 controls were consecutively selected from the database to match the age and gender distribution of the OSA participants. The two groups were not Body Mass Index (BMI) matched; the average BMI was 31 kg/m^2 in the OSA group indicating an obese cohort, compared to 25 kg/m^2 indicating an overweight control cohort.

Table 4-1 DEMOGRAPHICS OF OSA AND AGE-MATCHED CONTROL GROUPS

	Control (n=19)	OSA (n=19)
Age (years)	47, range 27-68	47, range 26-68
Gender (male: female)	15:4	15:4
BMI (kg/m^2)	25, range 18-31	31, range 22-41
AHI	NA	45, range 17-90
ESS	NA	9, range 2-16

Data presented as mean with range, or count. AHI, Apnoea-Hypopnoea Index; BMI, Body Mass Index; ESS, Epworth Sleepiness Scale; OSA, Obstructive Sleep Apnoea.

PROMs of Swallowing

Twenty six percent (5/19) of the OSA group reported symptomatic dysphagia (SSQ > 234). The total SSQ score was significantly higher in the OSA cohort compared with healthy controls (median = 116, IQR [70, 242] vs median = 42 [20, 66], Mann Whitney U Test F= 3.085, p <0.002, Figure 4.1).

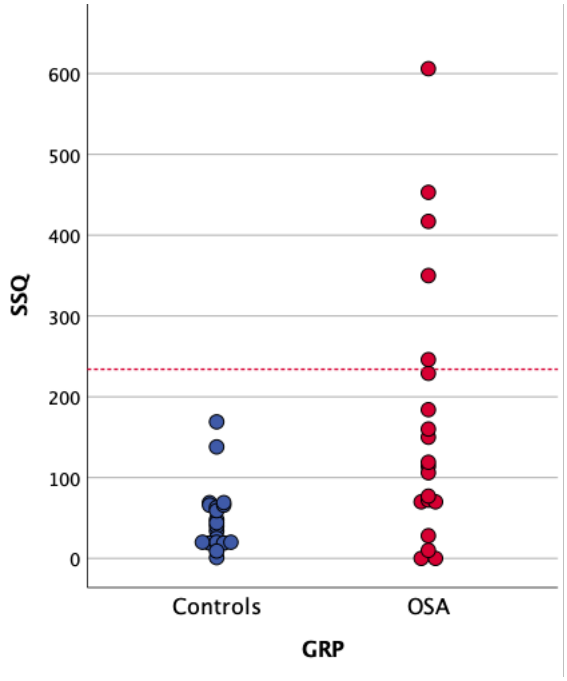

Figure 4-1 SCATTERPLOT SHOWING THE DISTRIBUTION OF SSQ SCORES OF THE CONTROL VS OSA GROUPS.

The blue line marks the median SSQ in the control group of 42 (IQR [20, 66]); the red line marks the significantly higher median SSQ in the OSA group of 116 (IQR [70,242]), approaching the symptomatic dysphagia cut-off value of 234. Five of 19 (26%) of the OSA group show symptomatic dysphagia (SSQ >234). Mann-Whitney U Test 3.085, p <0.002.

SSQ, Sydney Swallow Questionnaire; OSA, Obstructive Sleep Apnoea; GRP, Group

VFSS

VFSS was performed in a sub-group of 9 OSA participants (concurrently with P-HRM-I). Premature spillage was observed in 11% (1/9). All OSA participants presented with a PAS score within normal limits (level of 1 or 2). Valleculae post-swallow residue, quantified using the NRRSv, was within normal limits for 8 participants. One had a valleculae post-swallow residue score of 0.2, considered indicative of abnormal function. Interestingly, this participant was asymptomatic for dysphagia with a SSQ score of 160. All participants had a normal pyriform sinus post-swallow residue score (NRRSp; Table 4.2).

Table 4-2 RAW DATA OF VFSS BOLUS FLOW OUTCOMES OF ASPIRATION AND PHARYNGEAL RESIDUE

Participant No.	PAS	NRRSv	NRRSp
11	2	0.06	0
12	2	0.001	0.02
13	2	0	0
14	2	0	0
15	2	0.06	0.02
16	1	0	0
17	2	**0.20**	0.02
18	1	0	0
19	2	0.05	0

NRRS, Normalised Residue Ratio Scale (v, vallecular; p, pyriform); PAS, Penetration-Aspiration Scale. Bold value represents an abnormal score.

P-HRM-I Core Metrics

UOS Relaxation and Opening Extent

UES IRP was significantly increased in the OSA group compared with healthy controls ($p<0.0001$). Significant pairwise differences were present for all test combinations except for 5 mL extremely thick liquids ($p<0.05$) (Figure 4.2; Table 4.3). Similarly, UES opening diameter was reduced in the OSA group when compared with controls ($p<0.0001$). Pairwise comparisons were significantly different in the OSA group versus controls, for 10 mL thin and 10 mL and 20 mL extremely thick liquids ($p<0.05$) (Figure 4.3; Table 4.3). UES relaxation time was reduced in the OSA group versus controls ($p<0.02$). However, there were no significant pairwise differences.

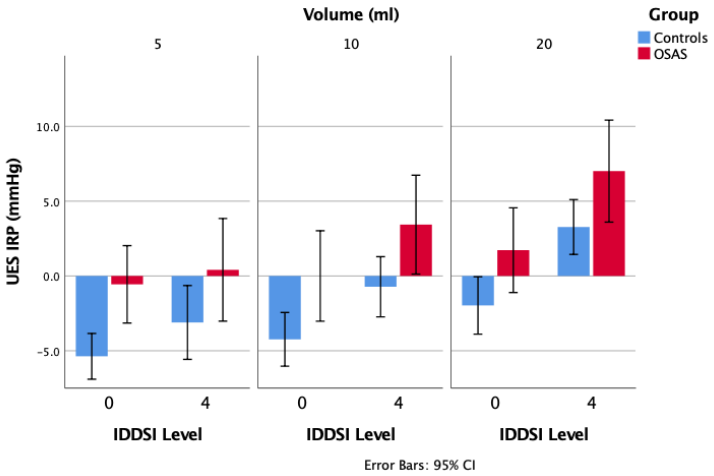

Figure 4-2 UOS INTEGRATED RELAXATION PRESSURE IN PARTICIPANTS WITH OSA COMPARED WITH AGE-MATCHED HEALTHY CONTROLS.

Bar graph illustrating mean and 95% CI for 5, 10, and 20 mL bolus volumes at thin (IDDSI level 0) and extremely thick (IDDSI level 4) consistencies for the OSA group (red) and control group (blue). UES IRP was significantly increased in the OSA group for all tested bolus conditions except 5 ml extremely thick liquid.

*** Denotes statistical significance (p<0.05, General Linear Mixed Modelling). IDDSI: International Dysphagia Diet Standardization Initiative; IRP: Integrated Relaxation Pressure; OSA: Obstructive Sleep Apnoea; UES: Upper Esophageal Sphincter.**

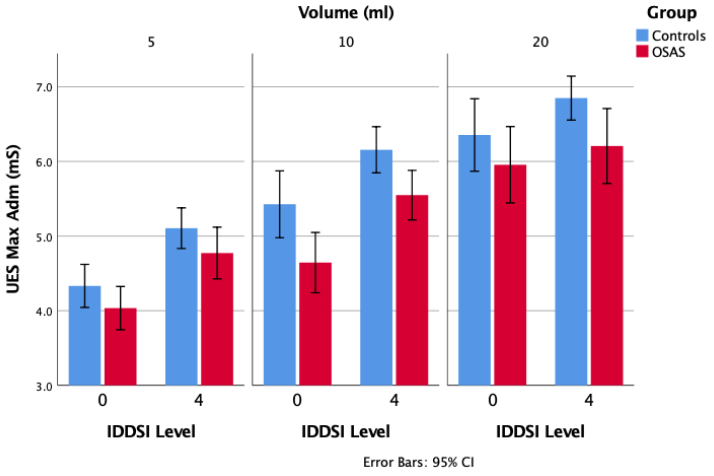

Figure 4-3 UOS OPENING EXTENT IN PARTICIPANTS WITH OSA COMPARED WITH AGE-MATCHED HEALTHY CONTROLS.

Bar graph illustrating mean and 95% CI for 5, 10, 20 mL bolus volumes at thin (IDDSI level 0) and extremely thick (IDDSI level 4) consistencies for the OSA group (red) and control group (blue). UES Opening Extent, measured by maximum admittance, was significantly reduced in the OSA group for 10 mL thin and extremely thick, and 20 mL extremely thick bolus conditions.

*** Denotes statistical significance (p<0.05, General Linear Mixed Modelling). IDDSI, International dysphagia diet standardization initiative; OSA, Obstructive sleep apnoea; Max Admin, maximum admittance; UES: upper esophageal sphincter.**

Hypopharyngeal Intrabolus Distension Pressure

The hypopharyngeal IBP was significantly increased in OSA participants compared with controls *(p* < 0.0001). Pairwise comparisons demonstrated significant increases for the OSA group for 5 ml and 20 mL thin liquids and 5 mL and 10 mL extremely thick liquids (*p* < 0.05; Table 4.3).

Pharyngeal Contractile Integrals (Velo-, Meso-, Hypo-)

Significant increases in VCI (*p* < 0.0001), HPCI (*p* < 0.0001) and PhCI (*p* < 0.0001) were present for the OSA group compared with healthy controls (Table 4.2). Pairwise comparisons were significantly increased for velopharyngeal and pharyngeal contractile integrals across all tested volumes and consistencies for the OSA group (Figure 4.4; Table 4.2). The HPCI showed a significant increase for 10 mL extremely thick liquids (*p* < 0.0001). The MCI did not differ between OSA participants and healthy controls (*p* = 0.11, Table 4.3).

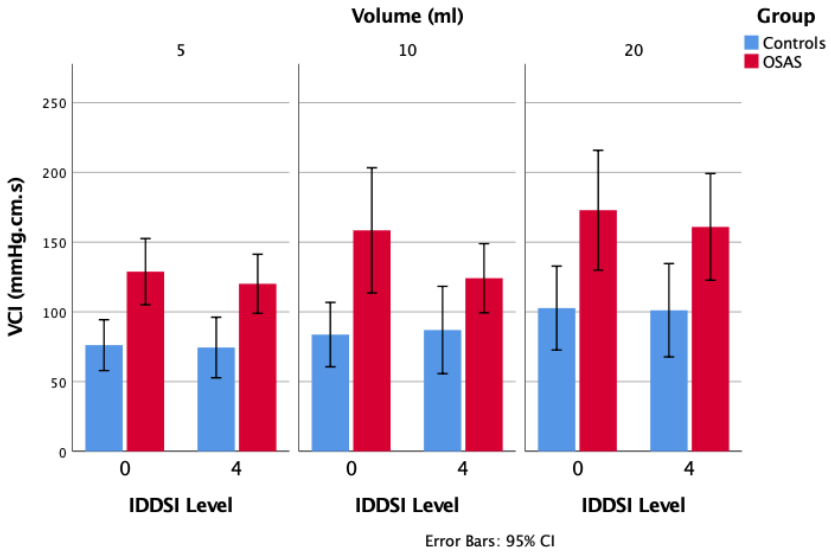

Figure 4-4 VELOPHARYNGEAL CONTRACTILE PRESSURE IN PARTICIPANTS WITH OSA COMPARED WITH AGE-MATCHED HEALTHY CONTROLS.

Bar graph illustrating mean and 95% CI for 5, 10, 20 mL bolus volumes at thin (IDDSI level 0) and extremely thick (IDDSI level 4) consistencies for the OSA group (red) and control group (blue). VCI was significantly increased in the OSA group for all tested bolus conditions.

*** Denotes statistical significance (p<0.05, General Linear Mixed Modelling). IDDSI: International Dysphagia Diet Standardization Initiative; OSA: Obstructive Sleep Apnoea; VCI: Velopharyngeal Contractile Pressure**

P-HRM-I Additional Metrics

The SRI was significantly elevated in the OSA group compared with controls (p<0.0001). Significant pairwise differences (increased SRIs) were present for all tested volumes of thin liquid and extremely thick liquids (p<0.05; Table 4.3).

The BPT did not differ between OSA participants and controls (p=0.6). The DCL was significantly shorter in OSA group compared with controls (p<0.002). Significant pairwise differences were present only for 20 mL thin liquid. UES BP, which measures the UOS pressure prior to swallow initiation, was reduced in the OSA group versus controls (p<0.003). Pairwise differences were present in 10 mL thin liquid only. When comparing the difference of thin versus thickened liquid, there were no differences observed in the OSA group compared with controls, who showed a significantly higher UES BP during thin liquid swallows (Figure 4.5; Table 4.3).

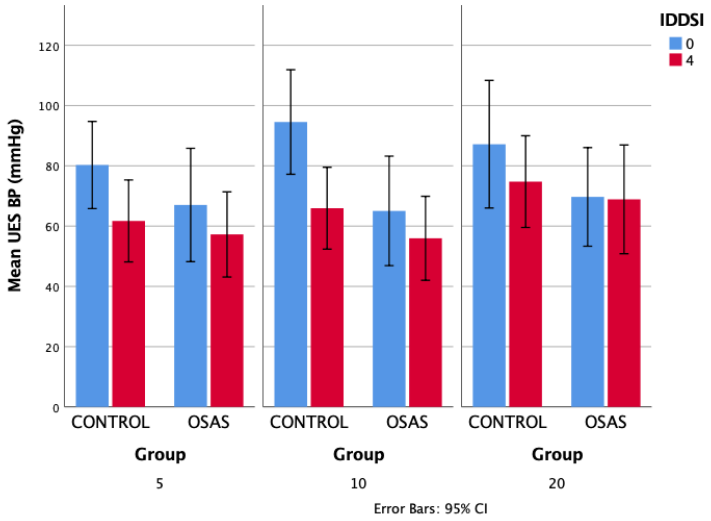

Figure 4-5 UES BASAL PRESSURE IN PARTICIPANTS WITH OSA COMPARED WITH AGE-MATCHED HEALTHY CONTROLS.

Bar graph illustrating mean and 95% CI for 5, 10, 20 mL bolus volumes at thin (IDDSI level 0, blue) and extremely thick (IDDSI level 4, red) consistencies for the OSA group and control group. The healthy control group demonstrates an increased UES basal pressure, measured prior to the swallow, for thin liquids compared to extremely thick liquids. In comparison, the OSA group have reduced UES basal pressure to thin liquids, particularly with 10 and 20 mL volumes.

*** Denotes statistical significance (p<0.05, General Linear Mixed Modelling). BP: Basal Pressure; IDDSI: International Dysphagia Diet Standardization Initiative; OSA: Obstructive Sleep Apnoea; UES: Upper Esophageal Sphincter.**

The post-swallow UOS contractility (UESCI) was reduced in the OSA group versus controls (p <0.026). However, no significant pairwise differences were identified. Proximal esophageal contractility (PCI) was not significantly different for the OSA group compared with controls (p=0.6; Table 4.3).

Table 4-3 P-HRM-I METRICS COMPARING THE OSA GROUP TO THE AGE-MATCHED HEALTHY CONTROL GROUP

P-HRM-I Core Metrics Mean (95% CI)				
Metric	**Control Group N=19**	**OSA N=19**	**F, p**	**Pairwise Comparisons of Bolus Volume and Viscosity**
Pharyngeal Contractile Integral **PhCI** (mmHg.cm.s)	287 (268, 307)	377 (357, 397)	F 39.9, p <0.0001	*thin liquids 5, 10 20 mL *extremely thick liquids 5, 10, 20 mL
[1]***Velopharyngeal Contractile Integral*** **VCI** (mmHg.cm.s)	87.5 (76,99)	144 (132,156)	F 69.6, p < 0.0001	*thin liquids 5 mL, 20 mL *extremely thick liquids 5, 10, 20 mL
Mesopharyngeal Contractile Integral **MCI** (mmHg.cm.s)	129 (119,139)	141 (131,151)	F 2.5, p = 0.111	ns
[1]***Hypopharyngeal Contractile Integral*** **HPCI** (mmHg.cm.s)	71 (63, 78)	92 (84,99)	F 18.2, p <0.0001	*extremely thick liquids 10 mL
Hypopharyngeal Intra-Bolus Pressure **IBP** (mmHg)	2.4 (1.1, 3.7)	6.5 (5.2,7.8)	F 18.9, p < 0.05	*thin liquids 5, 20 mL *extremely thick liquids 5, 10 mL
UES Maximum Admittance **UES Max Ad** (mS)	5.7 (5.6,5.8)	5.2 (5.0, 5.3)	F 23.5, p <0.0001	*thin liquids 10 mL *extremely thick liquids 10, 20 mL
UES Integrated Relaxation Pressure **UES IRP**	-2.0 (-3.0, 1.0)	2.0 (1.0, 3.0)	F 32.1, p <0.0001	*thin liquids 5, 10, 20 mL *extremely thick liquids 10, 20 mL

(mmHg)				
UES relaxation time **UES relax time** (s)	0.57 (0.55, 0.58)	0.54 (0.52, 0.56)	F 5.0, p <0.025	ns
P-HRM-I Additional Metrics **Mean (95% CI)**				
[1]***Swallow Risk Index*** **SRI**	1.9 (1.0, 2.7)	3.6 (2.7-4.5)	F 20.7, p <0.0001	*thin liquids 5, 10, 20 mL *extremely thick liquids 5 mL
[1]***Bolus Presence Time*** **BPT** (s)	0.7 (0.6,0.8)	0.7 (0.6, 0.8)	F 0.2, p =0.619	ns
Distension-Contraction Latency **DCL** (s)	0.51 (0.49, 0.52)	0.47 (0.46, 0.49)	F 10.0, p <0.002	*thin liquids 20 mL
UES basal pressure (mmHg)	77 (71,84)	64 (58,70)	F 8.8, p <0.003	* thin liquids 10 mL
UES Contractile Integral **UESCI** (mmHg.cm.s)	523 (483,563)	458 (417,598)	F 5.0, p <0.026	ns
[1]***Proximal Esophageal Contractile Integral*** **ProxEsCI** (mmHg.cm.s)	364 (326,401)	304 (265,342)	F 0.1, p = 0.675	ns

The table displays the main effects of General Linear Mixed Modelling (GLMM) with F statistic and P values. Pairwise comparisons with Bonferroni adjustment are presented comparing the OSA group to age-matched control group for each bolus condition. 1 denotes measures that were log transformed prior to GLMM. * denotes significance (p <0.05). pairwise comparisons of tested bolus conditions across volumes (5, 10 or 20 mL) and viscosity (thin [IDDSI 0] and extremely thick [IDDSI 4] liquids). ns denotes not significant result.

4.4 Discussion

This is the first known study investigating dysphagia using P-HRM-I technology in participants diagnosed with moderate to severe OSA. The main findings of this study were: (1) 25% of participants with moderate-severe OSA were symptomatic of dysphagia, and (2) participants with OSA presented with an altered biomechanical swallowing pattern when compared with healthy controls. Participants with OSA demonstrated reduced UOS opening diameter and UOS restriction during bolus flow, elevated bolus distension pressure at the hypopharynx, and increased velopharyngeal contractile pressures. These findings suggest that the OSA participants presented with evidence of UOS dysfunction with associated changes in distention pressure and contractility.

Twenty-six percent of participants with moderate-severe OSA were found to have elevated scores of self-reported dysphagia. This is comparable with published reports (660, 661), with one large study (n=507) finding 16% of middle-aged OSA patients self-reporting dysphagia (661). Although not all of the participants with OSA presented with symptomatic dysphagia, there was a significantly increased median dysphagia symptom score reported when compared with healthy controls. This observation is consistent with previous studies (310). Interestingly, there is no current evidence to indicate a negative impact of the presence of dysphagia on health related quality-of-life measures in patients with OSA (662). This suggests that swallowing changes in patients with OSA may be minor and sub-clinical in nature. However, when the OSA associated swallowing alterations are compounded with the known age-related deterioration of the swallowing mechanism (663), this may result in an exacerbation of presenting dysphagia. This requires further investigation.

Participants with OSA demonstrated reduced UOS opening extent, as measured by UES Max Adm when compared with healthy controls. Given the known biomechanical relationship of hyolaryngeal movement resulting in increased traction and opening of the UOS (104), reduced UOS opening may correlate with previously reported findings of reduced hyolaryngeal contraction times in an OSA cohort (664). In another study, reduced UOS opening extent was hypothesised to represent either reduced pharyngeal contractility pressure and/or UOS bolus flow restriction (591). The participants with OSA in our study had contractility pressure measures within or above the normal range. It is therefore likely that reduced UOS opening extent in the OSA cohort is representative of UOS bolus flow restriction. An additional measure indicative of UOS restriction during bolus flow is an increase of UOS relaxation pressure during

swallowing (UES IRP) (497, 665). A significant increase in UES IRP was observed in the OSA cohort when compared with healthy controls.

Hypopharyngeal IBP, an indirect measure of UOS bolus flow restriction (497), measures the bolus distension pressure at the hypopharynx. Increased IBP values may signify reduced UOS opening extent and/or reduced UOS distension pressure (159, 499). Increased IBP was observed in the OSA cohort when compared with healthy controls. There are numerous potential causes that result in increased IBPs, such as altered swallow modulation or anatomical causes, such as cricopharyngeal bar or UOS fibrosis (665, 666). However, in the nine VFSSs conducted, anatomical abnormalities were not observed. This is further indication that the participants with OSA experienced UOS bolus flow restriction most likely due to altered swallow modulation. Multiple studies have analysed UOS bolus flow restriction, identifying its presence in healthy participants when swallowing increased viscous liquids compared with thin liquids (159, 667). Collectively, reduced UOS opening extent and UOS bolus flow restriction findings most likely represent a neuroregulatory impairment of altered UOS function associated with OSA. This type of impairment may cause the central nervous system to produce a swallowing motor response that less efficiently accommodates the bolus volume and consistency (179).

The mismatched BMI of the OSA cohort when compared with the healthy controls is an additional consideration when interpreting the altered UOS metrics. The OSA group had a higher BMI (mean of 31 kg/m^2, indicative of obesity), compared with the healthy controls (mean BMI of 25 kg/m^2, indicative of overweight). It is largely accepted that fat deposits in the lateral pharyngeal wall and posterior tongue are associated with upper airway collapsibility in patients with OSA (668). This may result in propulsion of liquid through a reduced space with associated increased intra-bolus pressure in the hypopharynx and UOS regardless of the UOS opening extent. Whilst this requires further exploration to discriminate between the effects associated with OSA and BMI, the altered UOS biomechanical measures, together with known peripheral sensory neural injury in patients with OSA (272, 669, 670), could suggest diminished sensory input to the brainstem central pattern generator, resulting in alterations of swallowing modulation.

The VCI, a measure of lumen occlusive pressure, was significantly increased in participants with OSA compared with healthy controls for all trialled consistencies. This indicates that there is an increased velopharyngeal pressure generation in the OSA cohort during swallowing. This finding may be representative of increased tissue volume of the retropalatal region, or a

compensatory response to observed reduced UOS opening extent and UOS bolus flow restriction. Velum collapsibility has been found in 81% of patients with OSA during sleep (671), which may account for the observed increased velopharyngeal contractile pressure in this OSA cohort. Velopharyngeal contraction is necessary for adequate pressure generation allowing for effective bolus clearance through the pharynx and upper oesophageal sphincter. Velopharyngeal contractile pressure and duration increases with increased volume during swallowing, in order to seal the nasal cavity eliminating nasal regurgitation (110, 579, 672), and contributes to the configuration of an enclosed pharyngeal chamber assisting with bolus propulsion (105). It is plausible that restricted bolus flow through the UOS may result in an adaptive response whereby increased velopharyngeal contraction generation is required for more effective pharyngeal bolus propulsion. A biomechanical association between the velopharynx and the UOS has previously been described. During neck flexion manoeuvres in healthy participants, stable velopharyngeal pressures and associated reduced UOS pressures were considered to function to assist in bolus clearance (673). Additionally, increased velopharyngeal pressures have been shown when body positioning is inverted (>90 degrees) demonstrating the adaptability of the pharyngeal swallowing mechanism (622). In contrast, in a human model study, UOS restriction via external cricoid pressure did not result in an increase in the velopharyngeal contractility (579). This may suggest that the increased velopharyngeal pressures are not biomechanically linked in response to the UOS bolus flow restriction, or could reflect the inability of the model to represent the neuromuscular deviations in UOS bolus flow restriction in humans. Interestingly, increased pharyngeal closure pressure during swallowing has also been demonstrated in people who are obese (674). This was hypothesised to result from increased fat deposit in the tongue base and altered hyoid bone positing with associated superiorly positioned epiglottis towards the soft palate (674).

Previous studies identified sensory impairment associated with swallowing dysfunction in patients with OSA (272, 278). One study found patients with OSA to have a prolonged latency to initiate a swallow, suggestive of a peripheral sensory impairment affecting the swallowing mechanism (279). In our study, participants with OSA were found to have significantly shorter DCL and significantly reduced UES BP (and unaffected by liquid viscosity) compared to controls. Shortened flow-timing measures have been observed in healthy participants in response to increased viscous liquids, which represents the slowed transit of the bolus through the pharynx resulting in a ‘late’ onset of the bolus arrival (544), reflecting the normal neuromodulation of the swallowing mechanism. The mechanical receptors in the oropharyngeal

mucosa detect afferent pressure, volume and viscosity stimulation, which is important for appropriate modulation of the swallowing motor output to provide for effective bolus accommodation (179, 667). In our study, the shortened DCL and reduced UES BP observed in the participants with OSA may indicate altered swallowing modulation; a finding that has similarly been shown in healthy participants following opioid administration (612). These findings further support previous literature that reported sensory impairment to be a contributing mechanism to altered swallowing associated with OSA (272, 278, 279).

Altered timing measures, such as the findings in our study, could also be explained due to the reduced hypopharyngeal space associated with excessive soft tissue and narrowed upper airways in patients with OSA. Obesity has been shown in a VFSS based study to be associated with increased premature spillage and pharyngeal clearance time (674). This may be associated with shortened DCL whereby the bolus arrives earlier prior to pharyngeal contraction. However, in the subset of participants with OSA in our study who underwent VFSS, premature bolus spillage was observed in only one participant (10%). This observation differs to previous studies, where the frequency of premature bolus spillage has been reported between 15-51% (275, 277, 664, 675). This discrepancy could be attributable to the acknowledged difficulty in accurately distinguishing premature spillage from delayed swallow initiation (676), which may be further exacerbated by unclear definitions (394). Additionally, the bolus position at the onset of the pharyngeal swallow in healthy controls is highly variable, (outlined in *Section 1.1.3*), with 90% of people initiating their swallow below the tongue base and mandibular ramus (93-95), which historically was considered to be representative of impaired swallow response. It is therefore necessary to interpret these findings with caution (247).

The biomechanical results presented here demonstrate the utility of P-HRM-I in broadening the current understanding of the pathophysiology of pharyngeal swallowing in patients with OSA. In a recently published systematic review investigating OSA and the association with dysphagia, approximately one-half of the studies utilised visual instrumental assessments and primarily reported bolus flow outcomes of penetration, aspiration and bolus residue (247). Whilst the reporting of these outcomes are necessary regarding the frequency of the dysphagia manifestations, absent or limited identification of the associated pathophysiological impairments leads to wide variability in the interpretation of the findings and subsequently limits treatment planning (471). An increased understanding of the application of P-HRM-I technology to isolate the pathophysiological mechanisms that contribute to abnormal bolus flow findings may facilitate the treating clinicians' interpretation of visual instrumental assessments.

There are several acknowledged limitations of this study: (1) our study was unable to compare the identified altered swallowing biomechanical features in those participants with OSA who were symptomatic and asymptomatic for dysphagia; (2) the two groups were not BMI matched, with a higher BMI in participants with OSA being a common observation. It is important to consider that in people who are obese, changes in pharyngeal swallowing function have been identified, including increased premature spillage and increased pharyngeal clearance time (674). Whilst there is little published data on pharyngeal P-HRM-I in relation to BMI, one adolescent study did not find a correlation (677); (3) visual instrumental assessment findings were only conducted in 9 of the 19 participants with OSA, reducing the ability to correlate any observed visual findings with P-HRM-I measures. Increased numbers of visual instrumental findings to correlate with P-HRM-I studies is important given the sub-clinical presentation of dysphagia in patients with OSA. Furthermore, utilising a protocol inclusive of the testing of solid textured foods may have revealed further distinctions on visual instrumental assessments that could be correlated with P-HRM-I findings; (4) although the present study utilised standardised and quantified measures of aspiration and residue in visual instrumental assessment, more detailed standard rating systems in the interpretation of VFSS observations may have revealed further correlations of the P-HRM-I metrics with VFSS metrics. This would assist in clinical translation of the findings. Notwithstanding, given the largely sub-clinical presentation of the swallowing dysfunction observed in the OSA cohort, P-HRM-I may be a more sensitive assessment of swallowing physiology in patient cohorts without overt dysphagia. Future studies should consider further exploration of the identified altered biomechanical features and consider the possibility of phenotypes of dysphagia biomechanical patterns, as well as hypothesis-driven protocols in the application of screening validation and/or interventional studies.

4.5 Conclusion

This study demonstrated the utility of P-HRM-I technology to elucidate contributory pathophysiological mechanisms in participants with moderate-severe OSA. These additional insights of key altered swallowing biomechanical measures include increased velopharyngeal contractile pressure generation, reduced UOS opening extent and bolus flow restriction through the UOS and shortened bolus flow timing. These abnormal measures suggest that the pathophysiological mechanisms contributing to dysphagia in OSA is consistent with (1) an impeded ability to modulate the oropharyngeal swallow to accommodate the bolus efficiently, and (2) increased velopharyngeal pressure generation, which could be representative of increased tissue volume at the retropalatal region, and/or a compensatory response to counteract the effects of reduced efficient bolus transport through the UOS.

In Chapter 4, P-HRM-I revealed novel biomechanical swallowing metrics in participants with moderate-severe OSA, providing new insight into the mechanistic alterations contributing to dysphagia in this cohort. The surgical management of patients with OSA has been increasing over time, however there are conflicting reports regarding the impact that surgery has on swallowing. The Flinders group described swallowing in a small group of patients following mUPPP+/-CCT surgery for the management of OSA using P-HRM-I (1). In the following Chapter, additional participants were enrolled in this dataset in order to better evaluate the biomechanical swallowing patterns in a larger cohort of participants following mUPPP +/- CCT surgery when compared with healthy controls, and provide a more robust understanding of the impact of this surgical technique on swallowing.

5. DYSPHAGIA ASSESSMENT FOLLOWING MULTI-LEVEL UPPER AIRWAY SURGICAL MANAGEMENT FOR OSA

5.1 Introduction

The surgical management of patients with OSA has expanded and evolved over time, with contemporary surgical techniques being associated with improved outcomes (287). Modified uvulopalatopharyngoplasty (mUPPP), a reconstructive technique of the soft palate to widen the pharyngeal cavity, and coblation channelling of the tongue (CCT), a procedure to stiffen the tongue base, are contemporary surgical techniques that together have been shown to reduce the severity of OSA as well as day-time sleepiness symptoms (*Section 1.3.2*) (281). Despite the positive functional outcomes associated with contemporary surgery, post-operative complications can still occur. Complications identified in two systematic reviews include dysphagia, globus sensation, dry pharynx, voice changes, smell and taste disturbance, and velopharyngeal insufficiency (248, 249). Understanding the incidence and types of complications is important in order to minimize their occurrence and ensure efficacious pre-operative patient counselling (287).

In general, the reported incidence of dysphagia following surgical intervention for OSA is 18-27% (248, 249). However, the literature describing the post-surgical assessment of swallowing often utilises non-validated self-reported measures of swallowing (287, 292, 293, 296-311). Several studies have utilised VFSS as a visual instrumental assessment of pharyngeal swallowing, with post-surgical abnormalities identified, including premature spillage (294, 295, 313), pooling in the vallecula (312), incomplete epiglottic inversion (312, 313), velopharyngeal insufficiency (312), laryngeal penetration and/or aspiration (312, 314), reduced tongue base retraction and reduced pharyngeal shortening (315) and reduced pharyngeal constriction times (290). Whilst these identified swallowing changes are noteworthy, they were not specific to the type of surgical procedure that was performed as a wide range of upper airway surgical techniques were included (290, 294, 295, 312-314).

The mUPPP+CCT surgery targets the anatomical regions of the velopharynx and mesopharynx. Therefore, it was postulated that changes in swallowing biomechanical measures at these levels would be apparent. Our group previously investigated swallowing post mUPPP+CCT using P-HRM-I technology and identified post-operative altered UOS function suggesting altered sensory modulation from the surgical impact at velopharynx (1). However, this was a pilot study

of a small cohort (n=12). The application of P-HRM-I to identify biomechanical swallow changes in a larger cohort of post-surgical patients when compared with healthy controls aims to provide further understanding of the impact of surgery on swallowing and potentially assist clinicians in identifying those patients who may be at an increased risk of post-operative dysphagia.

Aim

To use P-HRM-I to assess the swallowing biomechanics of participants following mUPPP+/-CCT surgery for OSA and compare these results to healthy controls.

5.2 Methods

Participants

Ethical approval was granted by the Southern Adelaide Clinical Human Research Ethics Committee (No. 283.11 and 156.18). Participants were prospectively enrolled between July 2016 - September 2020. Participants who had undergone mUPPP and/or CCT for the management of OSA and/or snoring were recruited from the Otolaryngology Head and Neck Surgery Unit at Flinders Medical Centre. Inclusion criteria: adult (>18 years), and a minimum of 6 months following upper airway surgery (mUPPP+/-CCT) for the management of OSA or snoring. Exclusion criteria: other pharyngeal or gastrointestinal surgery, gastroesophageal reflux disease, allergy to local anaesthesia, pregnancy, uncontrolled diabetes or blood pressure, and a neurological diagnosis. Data from this round of participant recruitment were added to the data from the previously published study (n=12) using the same inclusion and exclusion criteria (1). Age- and gender-matched control data were acquired from an existing laboratory database (544). BMI-matched data was unavailable. Refer to *Section 3.4.3.4* for details of the healthy control data.

Surgical Technique

The mUPPP was performed under general anaesthesia and involved the following techniques, as previously described (281, 288): bilateral tonsil and supra-tonsillar fat resection, division of posterior pillar mucosa and musculature at the junction of upper third/lower two-thirds, advancement of the upper part of the posterior pillar musculature into the superolateral velopharyngeal port, and 50% to 75% resection of the uvula to create a neo-uvula. The coblation channelling of the tongue involved the use of a Reflex 55 or SP plasma wand (Arthrocare Corp, Austin, TX, USA) at a power setting of 6, for 15 sec per channel. A maximum of 7 channels were created along the anterior tongue, comprising 3 midline channels and up to 2 lateral channels on each side (281, 288).

PROMs

The SSQ was used to assess patient-reported outcome measures of swallowing (651) (*Section 3.4.1*). The ESS was used to assess daytime sleepiness (659)(*Section 4.2*).

Swallowing Assessment

The standard P-HRM-I protocol was followed. Data of the thin liquid swallows of 5, 10 and 20 mL volumes were added to the data from the published pilot study (n=12) (1). The data acquired from the extremely thick liquid swallows was not incorporated with the pilot data due to differences in bolus medium composition (different manufacturers). These differing products may affect the impedance-derived measures and thereby potentially confounding interpretation of these measures.

Statistical Analysis

PROM scores and P-HRM-I metrics from patients following mUPPP+/-CCT were compared with healthy control group data. Refer to *Section 3.5* for details of the statistical analysis.

5.3 Results

Twenty-one post-surgical participants were included and compared with an age- and gender-matched control group (n=21), with group demographics presented in Table 5.1. 63% (14/21) had severe OSA (AHI >30 events/h sleep),14% (3/21) had moderately severe OSA (AHI between 15-30 events/h sleep), 9% (2/21) had mild OSA, and (9%) 2/21 did not have OSA but reported snoring. Excessive daytime sleepiness was reported in 29% (6/21) of the participants. 95% (20/21) underwent mUPPP+CCT and 5% (1/21) underwent CCT alone. The average time of the P-HRM-I assessment was 19 months (range 6-65 months) following surgery. The BMIs were unable to be matched between groups: the average BMI was 31 kg/m^2 in the participant group (indicating an obese cohort); the average BMI in the controls was 26 kg/m^2 (indicating an overweight cohort).

Table 5-1 DEMOGRAPHICS OF POST-SURGERY PARTICIPANTS COMPARED WITH AGE- AND GENDER-MATCHED HEALTHY CONTROLS.

	Post-Surgery Participants (n=21)	Controls (n=21)
Age (years)	51, range 28-68	51, range 28-68
Gender (male:female)	14:7	14:7
BMI (kg/m^2)	31, range 22-49	26, range 20-31
AHI	49, range 8-89	n/a
ESS	8, range 4-14	n/a
Surgery type (mUPPP+CCT:CCT alone)	20:1	n/a
Time lapse since surgery (months)	19, range 6-65	n/a

Shown are the means and ranges of THE POST-SURGERY PARTICIPANTS COMPARED WITH HEALTHY CONTROLS.

BMI: Body Mass Index; mUPPP+CCT: modified Uvulopalatopharyngoplasty and Coblation Channelling of the Tongue; CCT: Coblation Channelling of the Tongue; AHI: Apnoea-Hypopnoea Index; ESS: Epworth Sleepiness Scale

Routine post-surgical polysomnography was conducted at 3-6 months following surgery. The pre- and post-surgical AHI and ESS scores were available in 15 of the 21 participants (six participants declined post-surgical overnight polysomnography). The AHI was significantly reduced following surgery (pre-surgical median = 44, IQR [31, 75] vs post-surgical median = 18, IQR [9, 58], $p<0.01$, Wilcoxon Signed Rank Test). Similarly, the ESS was also significantly reduced following surgery (pre-surgical median = 9, IQR [5, 11] vs post-surgical median = 5, IQR [3, 6], $p < 0.05$, Wilcoxon Signed Test).

PROMs of Swallowing

Thirty three percent (7/21) of the post-surgery group reported symptomatic dysphagia (SSQ >234). The total SSQ score was significantly greater in the post-surgical cohort compared with healthy controls (Figure 5.1).

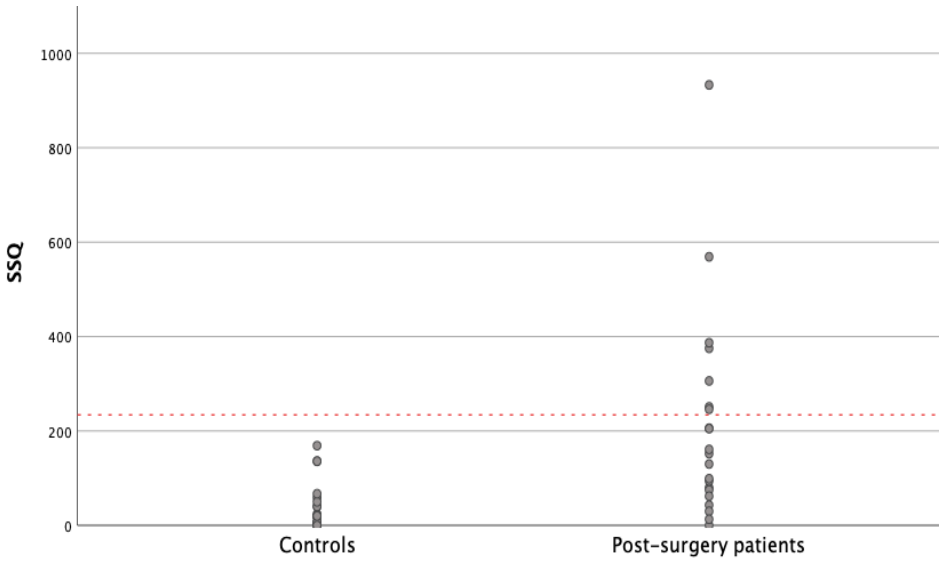

Figure 5-1 SCATTERPLOT DISPLAYING THE DISTRIBUTION OF SSQ SCORES OF THE CONTROL VS POST-SURGERY GROUPS.

7/21 (33%) of the Post-Surgery group presented with symptomatic dysphagia (SSQ>234). The blue line indicates the median SSQ of the control group of 20 (IQR [7, 54]); the red line indicates the significantly higher median SSQ of the Post-Surgery group of 152 (IQR [69,279]), approaching the SSQ symptomatic dysphagia cut-off value of 234. Mann-Whitney U Test -3.841, p <0.001.

SSQ, Sydney Swallow Questionnaire; GRP, Group

P-HRM-I Core Metrics

Data of the post-surgical group compared with age- and gender- matched controls are presented in Table 5.2.

Table 5-2 P-HRM-I METRICS COMPARING THE POST-SURGERY GROUP TO THE AGE- AND GENDER-MATCHED HEALTHY CONTROL GROUP.

P-HRM-I Core Metrics Mean (95% CI)

Metric	Control Group (n=21)	Post-Surgery Group (n=21)	F, p	Pairwise differences across volumes (5, 10 and 20 mL) of IDDSI 0
Pharyngeal Contractile Integral PhCI mmHg.cm.s	292 (262, 321)	347 (317, 376)	6.709 p<0.011	ns
Velopharyngeal Contractile Integral VCI mmHg.cm.s	93 (77, 110)	148 (131, 164)	21.282 p<0.001	*all volumes
Mesopharyngeal Contractile Integral MCI mmHg.cm.s	128 (115, 140)	148 (100, 125)	p=0.103	ns
Hypopharyngeal Contractile Integral HPCI mmHg.cm.s	71 (62, 79)	79 (70, 87)	p=0.180	ns
Hypopharyngeal Intra-Bolus Pressure IBP mmHg	1.9 (0.1, 3.7)	5.6 (3.8, 7.5)	F=8.266 p<0.05	*5 mL only
UES Integrated Relaxation Pressure UES IRP mmHg	-3 (-4, -2)	1 (0.3, 3)	F=33.976 p<0.001	*all volumes
UES Maximum Admittance UES Max Ad mS	5.3 (5.1, 5.6)	5.5 (5.2, 5.7)	p=0.347	ns
UES relaxation time UES relax time s	0.58 (0.56, 0.6)	0.55 (0.52, 0.57)	p=0.076	ns

Shown are the main effects of General Linear Mixed Modelling (GLMM) with F statistic and P values. Pairwise comparisons with Bonferroni adjustment are presented comparing the Post-Surgery group to the age- and gender-matched control group for each bolus condition*denotes significance (p<0.05) pairwise comparisons of tested bolus conditions across volumes (5, 10 or 20 mL). ns denotes not significant result.

UOS Relaxation and Opening Extent

UES IRP was significantly higher in the post-surgery group compared with healthy controls (p<0.001, Table 5.2). Significant pairwise differences were present for all volumes (p<0.05, Figure 5.2). UOS opening diameter was not significantly different in the post-surgery group

versus controls (p=0.347). Although UOS relaxation time was shorter in the post-surgical group versus controls, this was not statistically significant (p=0.076).

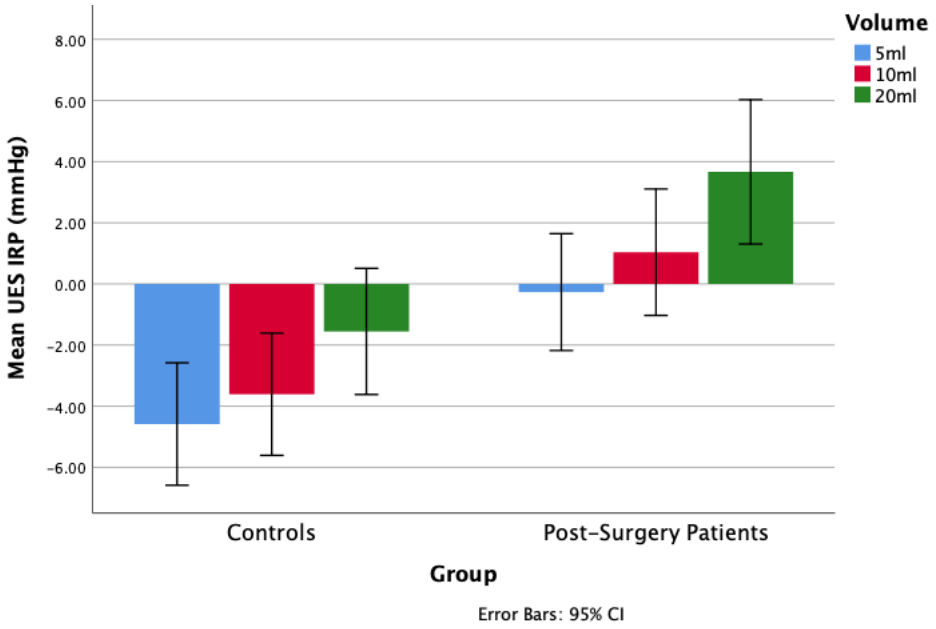

Figure 5-2 UES INTEGRATED RELAXATION PRESSURE IN THE POST-SURGERY COHORT COMPARED WITH AGE- AND GENDER-MATCHED HEALTHY CONTROLS.

Bar graph illustrating mean and 95% CI for 5, 10, 20 mL bolus volumes (blue, red and green, respectively) at thin (IDDSI level 0) liquid consistency for post-surgery and control group. the post-surgery group have higher UES integrated relaxation pressure, measured during bolus movement through the UOS, across all tested volumes.

*** Denotes statistical significance (p<0.05, General Linear Mixed Modelling). IRP: Integrated Relaxation Pressure; IDDSI: International Dysphagia Diet Standardization Initiative; UES: Upper Esophageal Sphincter**

Hypopharyngeal Intrabolus Distension Pressure

The hypopharyngeal IBP was significantly higher in post-surgery participants compared with controls (p<0.05). Pairwise comparisons were significant for 5 mL thin liquids (Table 5.2).

Pharyngeal Contractile Integrals (Velo-, Meso-, Hypo-)

The velopharyngeal contractile integral (VCI) and the pharyngeal contractile integral (PhCI) were significantly higher in the post-surgical group compared with the control group (p<0.001

and p<0.01, respectively; Table 5.2). For the VCI, pairwise comparisons were significant across all volumes (Figure 5.3). Although the hypopharyngeal contractile integral (HPCI) and mesopharyngeal contractile integral (MCI) were higher in the post-surgical participants when compared to healthy controls, this was not significant (p=0.180 and p=0.103, respectively; Table 5.2).

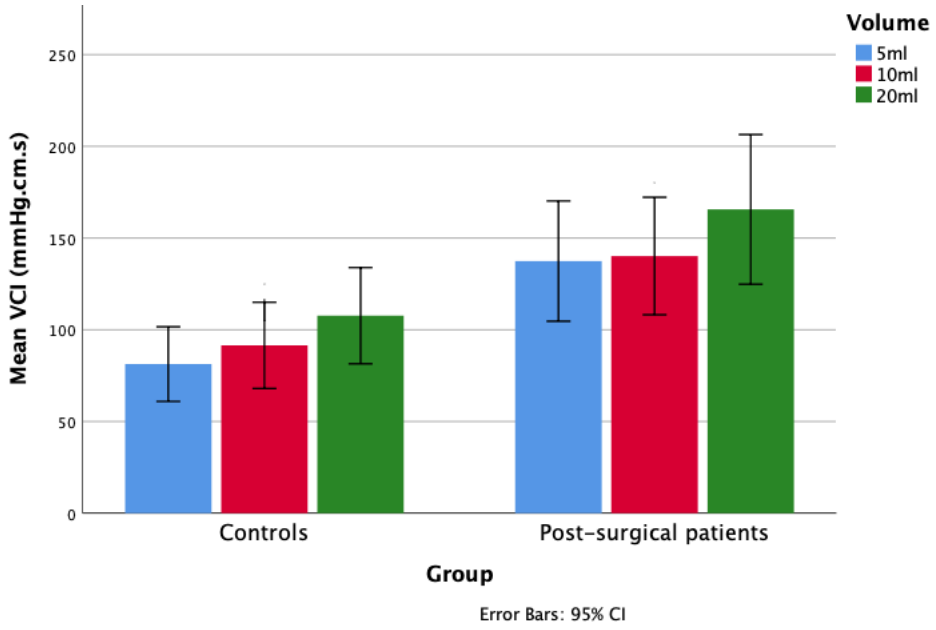

Figure 5-3 VELOPHARYNGEAL CONTRACTILE PRESSURE IN THE POST-SURGERY COHORT COMPARED WITH AGE- AND GENDER-MATCHED HEALTHY CONTROLS.

Bar graph illustrating mean and 95% CI for 5, 10, 20 mL bolus volumes (blue, red and green, respectively) at thin (IDDSI level 0) liquid consistency for post-surgery and control groups. VCI was significantly higher in the post-surgery group for all tested bolus conditions

*** Denotes statistical significance, post-surgical group vs control group (p<0.05, General Linear Mixed Modelling). IDDSI: International Dysphagia Diet Standardization Initiative; VCI: Velopharyngeal Contractile Pressure**

P-HRM-I Additional Metrics

P-HRM-I Additional Metrics are presented in Table 5.3.

Table 5-3 P-HRM-I ADDITIONAL METRICS COMPARING THE POST-SURGERY GROUP TO THE AGE- AND GENDER-MATCHED HEALTHY CONTROL GROUP.

P-HRM-I Additional Metrics Mean (95% CI)

Metric	Control Group (n=21)	Post-Surgery Group (n=21)	F, p	Pairwise differences across volumes (5, 10 and 20 mL) of IDDSI 0
[1]**Swallow Risk Index SRI**	0.005 (-0.96, 0.1)	0.193 (0.09, 03)	F=6.667 p<0.011	*5 mL only
Velopharyngeal to Tongue Base Integral VTI mm.Hg.cm.s	221 (197, 245)	261 (237, 285)	F=5.312 p<0.023	ns
Bolus Presence Time BPT s	0.73 (0.68, 0.78)	0.63 (0.58, 0.67)	F=9.411 p<0.003	*10 and 20 mL only
Distension-Contraction Latency DCL s	0.533 (0.51, 0.56)	0.47 (0.44, 0.49)	F=13.248 p<0.001	*20 mL only
[1]**Peak Pharyngeal Pressure** mmHg	2.12 (2.06, 2.17)	2.12 (2.06, 2.16)	p=0.83	ns
[1]**UES basal pressure** mmHg	1.86 (1.80, 1.93)	1.77 (1.70, 1.84)	p=0.056	ns
UES Contractile Integral UESCI mmHg.cm.s	501 (446, 556)	442 (387, 497)	p=0.140	ns
[1]**UES Peak Pressure UES Peak P** mmHg	2.42 (2.38, 2.47)	2.37 (2.32, 2.41)	p=0.093	ns
Proximal Esophageal Contractile Integral ProxEsCI mmHg.cm.s	2.87 (246, 329)	295 (253, 336)	p=0.86	ns

Shown are the main effects of General Linear Mixed Modelling (GLMM) with F statistic and P values. Pairwise comparisons with Bonferroni adjustment are presented comparing the Post-Surgery group to the age- and gender-matched control group for each bolus condition. 1 denotes measures that were log transformed prior to GLMM. *denotes significance (p<0.05) pairwise comparisons of tested bolus conditions across volumes (5, 10 or 20 mL). ns denotes not significant result.

The Swallow Risk Index (SRI) was significantly elevated in the post-surgical group compared with controls ($p<0.01$; Table 5.3). Pairwise differences were present for 5 mL volume only ($p<0.05$; Table Figure 5.4).

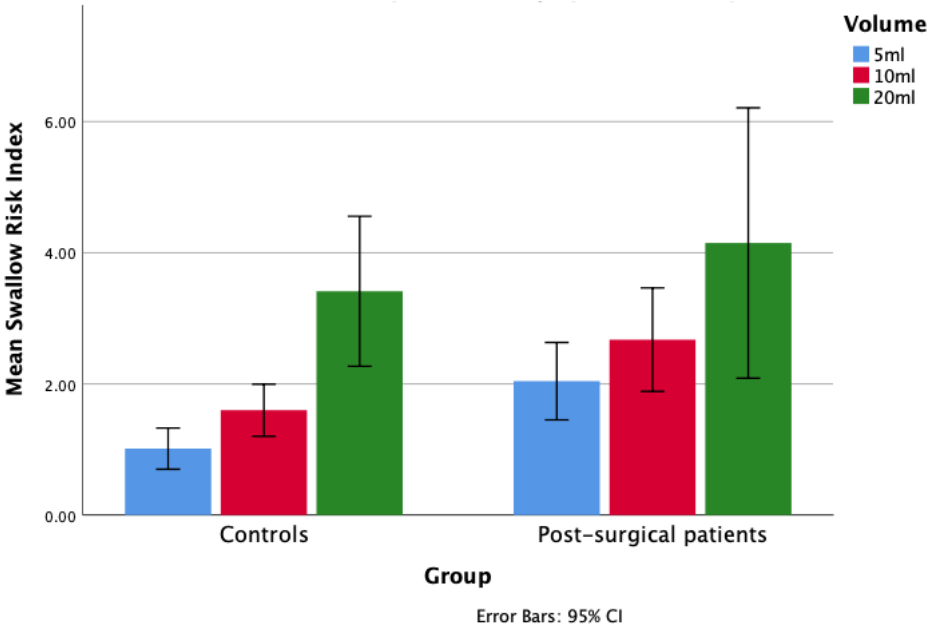

Figure 5-4 SWALLOW RISK INDEX (SRI) IN THE POST-SURGERY COHORT COMPARED WITH AGE- AND GENDER-MATCHED HEALTHY CONTROLS.

Bar graph illustrating mean and 95% CI for 5, 10, 20 mL bolus volumes (blue, red and green, respectively) at thin (IDDSI level 0) liquid consistencies for post-surgery and control groups. SRI was significantly higher in the post-surgery group for 5 mL thin liquid.

*** Denotes statistical significance, post-surgical group vs control group ($p<0.05$, General Linear Mixed Modelling). IDDSI: International Dysphagia diet Standardization Initiative; SRI: Swallow Risk Index**

The bolus presence time (BPT) was reduced in the post-surgical participants compared with controls ($p<0.01$; Table 5.3). Pairwise comparisons were significant for 10 and 20 mL volumes ($p<0.05$; Figure 5.5). Similarly, the distension-contraction latency (DCL) was significantly reduced in post-surgery participants compared with healthy controls ($p<0.0001$; table 5.3). Significant pairwise differences were present for 20 mL thin liquid. Although the post-surgery cohort presented with reduced UOS basal pressure compared with healthy controls, this was not significant ($p=0.056$; Table 5.3).

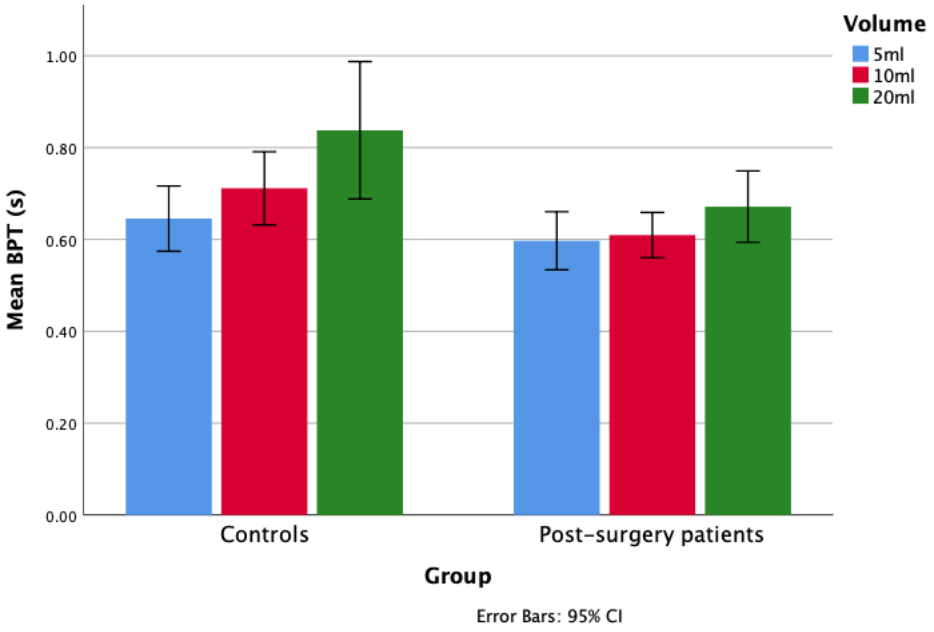

Figure 5-5 BOLUS PRESENCE TIME IN THE POST-SURGERY COHORT COMPARED WITH AGE- AND GENDER-MATCHED HEALTHY CONTROLS.

Bar graph illustrating mean and 95% CI for 5, 10, 20 mL bolus volumes (blue, red and green, respectively) at thin (IDDSI level 0) liquid consistency for post-surgery and control groups. BPT was significantly reduced in the post-surgery group for 10 and 20 mL thin liquids.

*** Denotes statistical significance ($p<0.05$, General Linear Mixed Modelling). IDDSI: International Dysphagia Diet Standardization Initiative; BPT: Bolus Presence Time.**

5.4 Discussion

This study contributes further understanding of the biomechanical swallowing changes following mUPPP+/-CCT surgery for OSA. The main findings of this study were: (1) 33% of post-surgical participants were symptomatic of dysphagia, and (2) altered biomechanical swallowing physiology, including higher UOS relaxation pressure, higher intra-bolus pressure, and increased velopharyngeal contractile pressures, were observed in the post-surgical cohort compared with age- and gender-matched healthy controls.

Dysphagia was self-reported in 33% of participants in the post-surgery cohort using validated PROMs of swallowing, with significantly higher scores when compared with healthy controls. This is comparable to one study that reported nearly 20% of patients complain of postoperative dysphagia following a broad range of surgical treatments for OSA management (287). Interestingly in that study, the multivariate logistical regression analysis showed that the UPPP technique was not an independent predictor of patient-reported dysphagia (287).

UOS relaxation pressure was elevated in the post-surgery cohort when compared with healthy controls, with significant pairwise comparisons observed across all tested bolus volumes. Additionally, the intra-bolus pressure, which is an indirect measure of UOS bolus flow restriction at the hypopharynx, was elevated in the post-surgery group. These results indicate an increase in UOS and hypopharyngeal distension pressures during swallowing, which is representative of UOS restriction during bolus flow (497, 579). Despite this finding of apparent UOS restriction, the post-surgery cohort had comparable UOS opening diameter, measured by UES maximum admittance, to healthy controls, therefore indicating UOS modulation was intact. Interestingly, these findings in this larger cohort of participants differ from our original published pilot study (n=12), where altered UOS modulation during swallowing was observed and considered an outcome of the surgical intervention (1). Duration of follow-up was considerably longer in the pilot study (average 2.5 years) without the AHI measured at the time of the swallow study and therefore these patients may have a degree of OSA relapse accounting for the return of UOS modulation. This is further explored in *Section 6.4* where swallowing is compared pre- and post-mUPPP+CCT surgery.

Increased velopharyngeal pressure generation during swallowing is evident in the post-surgical cohort compared to healthy controls, which is similar to the findings observed in the OSA cohort (*Section 4.3*). This suggests that the elevated velopharyngeal pressures observed in this post-surgical cohort may represent changes due to pre-existing OSA rather than being caused by the

surgery. It has been hypothesised that soft tissue volume reduction during mUPPP+CCT surgery is the predominant contributory factor to reduced OSA severity and improved self-reported sleepiness (288). In one study, reduced pharyngeal constriction times were observed using VFSS in patients (n=10) following UPPP, and attributed to a reduction of excess pharyngeal tissue (290). Further, an 18% reduction in soft palate volume was demonstrated on MRI following a more extensive hemiglossectomy, limited pharyngectomy and UPP procedure using trans-oral robotic surgery (TORS) (n=19) (678). In contrast, another study reported no significant change in soft tissue volume observed on MRI (n=43) 6 months following mUPPP+CCT surgery (679) suggesting that the mUPPP technique alters the upper airway collapsibility without excessive tissue resection (679). This could explain the sustained elevated velopharyngeal contractile pressures observed in this post-surgical cohort, which were also evident in patients with OSA (*Chapter 4*). The findings from our study suggest that the mechanism for altering airway collapsibility in patients with OSA may not be excessive tissue reduction as originally presumed, but instead be due to changes in pharyngeal soft tissue tension that is reflective of the contemporary surgical technique.

The hypopharyngeal and mesopharyngeal contractile integrals were not statistically different in the post-surgical group compared with healthy controls. These findings suggest that the radiofrequency tongue base treatment (CCT) may increase tongue stiffness, but not reduce soft tissue volume at the tongue base, thereby having minimal effect on mesopharyngeal contractile pressures. Furthermore, these findings are consistent with other studies that did not report significant reduction in tongue base volume following radiofrequency treatment (679, 680). This is further discussed in *Section 6.4*, when swallowing function is compared pre- and post-mUPPP+CCT surgery.

The post-surgery cohort demonstrated reduced bolus presence time when compared with the healthy controls. In this current study, the distension-contraction latency was significantly shortened in the post-surgery group compared with healthy controls for 20 mL volume of thin fluids only. However, in *Chapter 4*, the OSA cohort demonstrated comparable bolus presence times to healthy controls. Collectively, these biomechanical swallowing findings of short BPT and DCL are consistent with bolus transiting through the pharynx more rapidly, which is in contrast to previous VFSS-derived studies. Prolonged bolus presence in the hypopharynx following upper airway surgical intervention for OSA has been reported (312, 313), which may result in increased risk of airway invasion (681). These contrasting swallowing outcomes may reflect the effect of different surgical approaches. The VFSS studies were published more than

15 years ago when more traditional surgical techniques of UPPP were performed, including complete uvula and excessive velar tissue resection (636), which may account for the increase in dysphagia observations. Contemporary surgical techniques, such as mUPPP and/or CCT are associated with fewer complications, including a lower incidence of dysphagia (248, 636).

These P-HRM-I derived findings provide a broader understanding of the changes in pharyngeal swallowing following contemporary surgical intervention for OSA. Additionally, the use of pharyngeal luminal pressure and impedance metrics of swallowing illustrates sub-clinical changes post-surgery, which is fitting with the current understanding of upper airway modification by contemporary surgical techniques (679, 680). These results support continued investigation into the effects of mUPPP+CCT on swallowing outcomes and provide further insight which can support efficacious patient counselling for surgeons.

The following limitations of this study are acknowledged: (1) the BMI of the comparison groups were not matched. A higher BMI in people with OSA is a common observation. Furthermore, obesity has been associated with changes in pharyngeal swallowing (674) which could affect the assessment results; (2) retrospective data were utilised from a published pilot study (1); (3) data from the extremely thick liquid swallows were not included due to differences in bolus medium composition and the potential to impact on impedance derived measures. Concurrent visual instrumental swallowing assessment could be considered in future studies, which would likely assist in further clinical translation of the P-HRM-I findings. Future studies should also consider further exploration of the identified altered biomechanical measures in the application of screening validation studies.

5.5 Conclusion

mUPPP+/-CCT surgery is associated with altered swallowing biomechanics characterised by elevated velopharyngeal contractile pressures, and UOS relaxation and intra-bolus pressures. P-HRM-I metrics expand the current understanding of the swallowing biomechanics following contemporary mUPPP+/-CCT surgery, providing insight into the potential mechanisms contributing to dysphagia. Further studies are required to investigate if alterations in swallowing function are resultant of the upper airway surgery or attributed to the pathogenesis of OSA.

While our findings presented in Chapter 5 provide novel insights, a limitation of the study was that it did not compare post-surgical swallowing outcomes to pre-surgical baseline in the same cohort. The prospective evaluation of swallowing pre- and post-upper airway surgical intervention for the management of OSA has not previously been conducted in relation to the mUPPP+CCT surgical technique. In the following Chapter, P-HRM-I was utilised as an interventional outcome measure to compare the swallowing biomechanics post-mUPPP+CCT surgery to pre-surgical baseline in a moderate-severe OSA cohort.

6. DYSPHAGIA ASSESSMENT IN PARTICIPANTS WITH OSA PRE- AND POST-MODIFIED UPPP+CCT SURGERY[2]

6.1 Introduction

Dysphagia has been reported following the surgical management for OSA. In Chapter 5, 33% of post-surgical participants were symptomatic of dysphagia following mUPPP+/-CCT surgery. Biomechanical alterations in swallowing physiology, such as higher UOS relaxation and intra-bolus pressures as well as increased velopharyngeal contractile pressures, were evident following surgery when compared with healthy age- and gender-matched controls (*Chapter 5*). However, alterations in swallowing were also identified in an OSA cohort who had not yet undergone surgical intervention (*Chapter 4*). Thus, the degree of biomechanical pharyngeal swallowing changes that may be attributed to upper airway surgery for OSA management compared with the pathogenesis of OSA itself, remains unknown.

Few studies have prospectively investigated swallowing function using visual instrumental assessments pre- and post-upper airway surgical intervention for OSA (290, 314). No significant differences in hyolaryngeal function with multi-level OSA surgery with concurrent UPPP + geniotubercle advancement were reported (314). In another study, minimal VFSS pharyngeal swallowing changes consisting of increased hyolaryngeal movement and reduced velopharyngeal movement time at 14-days post-surgery were observed but returned to pre-operative baseline measures at one month (290). Interestingly, those patients who had undergone an UPPP (n=10) presented with persistent reduced pharyngeal constriction time at one month post-surgery compared with baseline measures, which was thought to reflect the reduction of excessive pharyngeal tissue (290).

The precise nature of the quantified P-HRM-I metrics allows for detection of subtle changes of swallowing physiology resulting from interventional treatments (27, 629, 631, 632). To date, no studies have utilised P-HRM-I to compare the post-surgical swallowing biomechanics to pre-surgical baseline in people with OSA. The application of P-HRM-I aims to provide further

[2] This data presented in this Chapter was **accepted for publication** in December 2021, Schar, MS. Omari, TI., Woods, CW., Doeltgen, S., Athanasiadis, T., Cock, C., Chai Coetzer, C-L., Eckert, D.J., & Ooi, E.H. Swallowing biomechanics pre-multi-level upper airway surgery for obstructive sleep apnea. *Journal of Clinical Sleep Medicine. doi 10.5664/jcsm.9824* (*Appendix 3*). It was accepted for an **oral presentation** at the Australian Society of Otolaryngology Head and Neck Surgery (ASOHNS) Virtual Conference, in September 2021.

understanding of the impact of surgery on swallow function and assist clinicians in identifying those patients who may be at an increased risk of post-operative dysphagia.

Aim

To compare swallowing outcomes in participants diagnosed with OSA prior to- and following-mUPPP+CCT surgery.

6.2 Methods

Participants

Ethical approval was granted by the Southern Adelaide Clinical Human Research Ethics Committee (No. 283.11 and 156.18). Participants were prospectively enrolled between July 2016 - September 2020. Participants were recruited following referral to the Otolaryngology Head and Neck Surgery Unit at Flinders Medical Centre or the private practices of Associate Professor Ooi and Dr Athanasiadis for suitability of upper airway surgery for the management of OSA. Inclusion criteria: adult (>18 years), planned for upper airway surgery (mUPPP+/-CCT) for the management of OSA (AHI >15). Exclusion criteria: other pharyngeal or gastrointestinal surgery, gastroesophageal reflux disease, allergy to local anaesthesia, pregnancy, uncontrolled diabetes or blood pressure, or a neurological diagnosis.

PROMs of Swallowing

The SSQ was used to assess patient-reported outcome measures of swallowing (651) (*Section 3.4.2*). The ESS was used to assess daytime sleepiness (659)(*Section 4.2*).

Swallowing Assessment

Swallowing assessments were conducted prior to surgery and at approximately 6 months following surgery. The standard P-HRM-I protocol and analysis of the P-HRM-I Core and Additional Metrics were followed (refer to *Section 3.4.3*).

Surgical Technique

The standard mUPPP+CCT (281, 288) surgery was performed under general anaesthesia, as described in *Section 5.2*.

Statistical Analysis

Analysis conducted according to *Section 3.5*. The main effects of surgery (time point) and baseline dysphagia on swallow biomechanics were determined using generalized linear mixed model whereby timepoint, volume and viscosity were included as repeated measures. GLMM statistics (F, *P*-value) were used to quantify and compare main effects. Patient-related outcome variables were compared pre- and post-surgery using Wilcoxon signed rank test. Data are otherwise presented as median (IQR).

6.3 Results

Participants

Pre- and post-surgical data were available for all 10 study participants. The median time for post-surgical P-HRM-I assessment was 9 months, ranging 6-13 months. Group demographics are presented in Table 6.1. Prior to surgery, seven participants had a diagnosis of severe OSA (AHI >30 events/h sleep) and three had moderate OSA (AHI between 15-30 events/h sleep). Excessive daytime sleepiness was reported in three participants (ESS >9). The median BMI value was 31 kg/m^2 (indicating an obese cohort).

Table 6-1PARTICIPANT CHARACTERISTICS

	Cohort N=10	
	Pre-Surgery ***Median [IQR]***	**Post-Surgery** ***Median [IQR]***
Age (years)	50 [36-65]	-
Gender (male:female)	7:3	-
BMI (kg/m^2)	31 [27, 36]	-
AHI	45 [29, 71]	26 [10, 72]
ESS	8.5 [6,11]	4 [2, 7]

BMI: Body Mass Index; AHI: Apnoea-Hypopnea Index; ESS: Epworth Sleepiness Scale.

Post-operative PSG was conducted at 3-6 months in seven participants, with three participants declining PSG due to improvement in sleepiness symptoms. Although the total AHI and the ESS values tended to decrease following surgery (Table 6.1), statistical significance was not demonstrated (P = 0.091 and P = 0.058, respectively).

PROMs of Swallowing

There was no significant change in median total SSQ scores following surgery (pre-surgery 149 [53, 447] vs post-surgery 168 [54, 247], P = 0.093, Figure 6.1). 70% (n=7) of participants did not have dysphagia symptoms (SSQ ≥234) at post-surgery follow up.

The three participants with pre-surgery dysphagia had a reduction in symptoms post-surgery, although two of these participants remained above the dysphagia score threshold (SSQ ≥234).

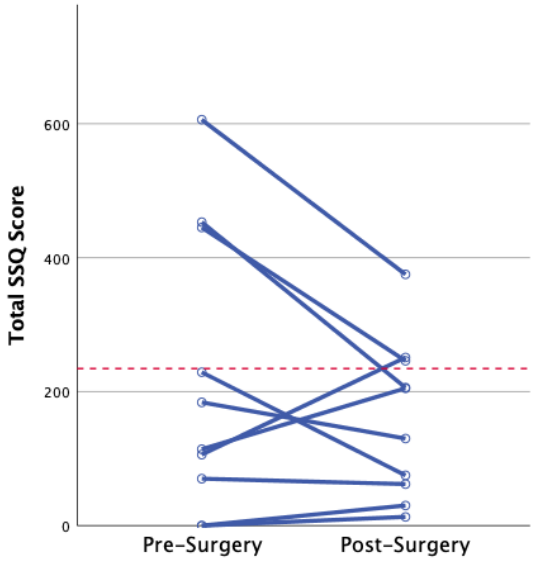

Figure 6-1 THE SELF-REPORTED DYSPHAGIA SYMPTOMS REPRESENTED BY SSQ SCORE PRE- AND POST-MUPPP+CCT SURGERY.

The red-dotted line marks the SSQ score of 234, representing the cut-off value of symptomatic dysphagia. Following mUPPP+CCT surgery, seven participants did not demonstrate symptomatic dysphagia. Of the three participants with symptomatic dysphagia pre-surgery, all showed a decrease in dysphagia symptoms post-surgery, although two remained above the cut-off line for symptomatic dysphagia.

P-HRM-I Metrics

All participants tolerated the P-HRM-I investigations, although two participants were unable to consume 20 mL extremely thick liquid bolus due to self-reported fullness. The pre- and post-surgery P-HRM-I Core and Additional Metrics are shown in Table 6.2

Table 6-2 BIOMECHANICAL MEASURES OF SWALLOWING PRE- AND POST-MUPPP+CCT FOR THE MANAGEMENT OF MODERATE-SEVERE OSA

P-HRM-I Core Metrics			
Metric	**Pre-Surgery N=10**	**Post-Surgery N=10**	**Main Effects of Surgery**
Pharyngeal Contractile Integral mmHg.cm.s	396 (374, 417)	361 (328, 395)	All Conditions: F 2.852, p = 0.094
Velopharyngeal Contractile Integral mmHg.cm.s	135 (123, 147)	137 (117, 157)	NS
Mesopharyngeal Contractile Integral mmHg.cm.s	148 (135, 161)	124 (112, 137)	All Conditions: F 6.771, p = 0.011* 20 mL Volume: F 4.573, p = 0.035*
Hypopharyngeal Contractile Integral mmHg.cm.s	113 (101, 125)	93 (84, 102)	All Conditions: F 6.713, *P* = 0.011*
Intra-Bolus Pressure mmHg	7.57 (6.44, 8.70)	5.65 (3.54, 7.76)	All Conditions: F 2.529, p = 0.115
UES Integrated Relaxation Pressure mmHg	5.15 (3.84, 6.46)	2.18 (1.16, 3.19)	All Conditions: F 12.615, p = 0.001* 5 mL Volume: F 2.666, p =0.047* 10 mL Volume: F 3.581, p =0.010* Thin: F 6.060, p =0.015* Thick: F 6.557, p =0.012*
UES Relaxation Time s	0.55 (0.53, 0.57)	0.56 (0.53, 0.58)	NS
UES Maximum Admittance mS	5.21 (5, 5.38)	5.39 (5.18, 5.59)	All conditions: F 1.724, p = 0.192
High-Resolution Pharyngeal Manometry Additional Metrics			
Swallow Risk Index [1]	2.56 (2.18, 2.93)	1.83 (1.35, 2.31)	All Conditions: F 6.909, p = 0.010* 20ml Volume: F 5.913, p = 0.017* Thick: F 6.112, p = 0.015*
Bolus Presence Time s	0.62 (0.58, 0.65)	0.61 (0.57, 0.64)	NS
Distension-Contraction Latency s	0.48 (0.46, 0.50)	0.46 (0.43, 0.48)	All Conditions: F 2.620, *P* = 0.108

UES Basal Pressure mmHg	74 (64, 84)	81 (69, 93)	NS
UES Contractile Integral mmHg.cm.s	487 (437, 536)	515 (460, 570)	NS
Proximal Esophageal Contractile Integral[1] mmHg.cm.s	308 (283, 333)	372 (314, 430)	NS

Shown are main effects of General Linear Mixed Modelling (GLMM) with F statistic and P values. Pairwise comparisons with Bonferroni adjustment presented pre- and post-surgery for each bolus condition. 1 denotes measures that were log transformed prior to GLMM. * denotes significance (p <0.05) pairwise comparisons of tested bolus conditions across volumes (5, 10 or 20ml) and viscosity (thin [IDDSI 0] and extremely thick [IDDSI 4] liquids). ns denotes not significant result. Is missing pairwise then nothing significance. Only significant pairwise comparisons are shown.

UES: Upper Esophageal Sphincter

P-HRM-I Core Metrics

Pharyngeal Contractile Integrals (Velo-, Meso-, Hypo-)

Velopharyngeal contractility (VCI) did not change following surgery (Table 6.2). There was a significant reduction of the mesopharyngeal contractility (MCI, p = 0.01, Table 6.2, Figure 6.2) and the hypopharyngeal contractility (HCI, p = 0.01, Table 6.2) following mUPPP+CCT. Pairwise comparisons showed that the reduction of the mesopharyngeal contractility was most pronounced during 20 mL swallows ($P < 0.05$, Table 6.2). Total pharyngeal contractility (PhCI) tended to reduce following the surgery however was not statistically significant (p = 0.09, Table 6.2).

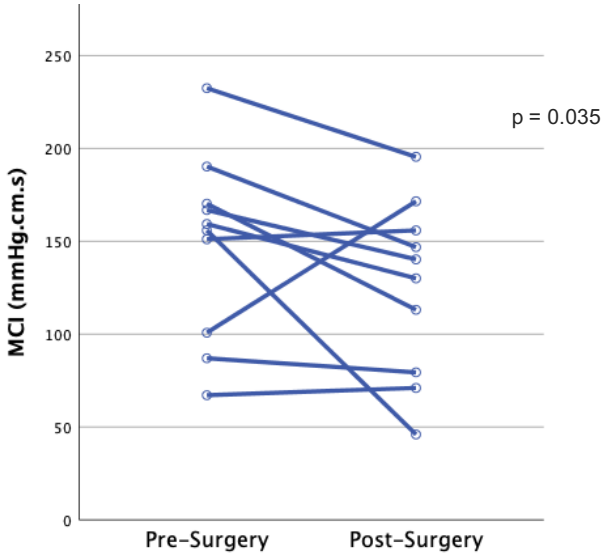

Figure 6-2 MESOPHARYNGEAL CONTRACTILE PRESSURES PRE- AND POST-MUPPP+CCT SURGERY OF A 10 ML VOLUME THIN FLUIDS.

There was a significant reduction of mesopharyngeal contractility post-surgery. The graph illustrates individual participant results: Six participants show a reduction in pressures post-surgery, while one participant shows and increase. Three appear largely unchanged between the two time points.

MCI: Mesopharyngeal Contractile Integral; mUPPP+CCT: Modified Uvulopalatopharyngoplasty and Coblation Channelling of the Tongue

Figure 6.3 displays one participant example of a swallow pre- and then post-mUPPP+CCT.

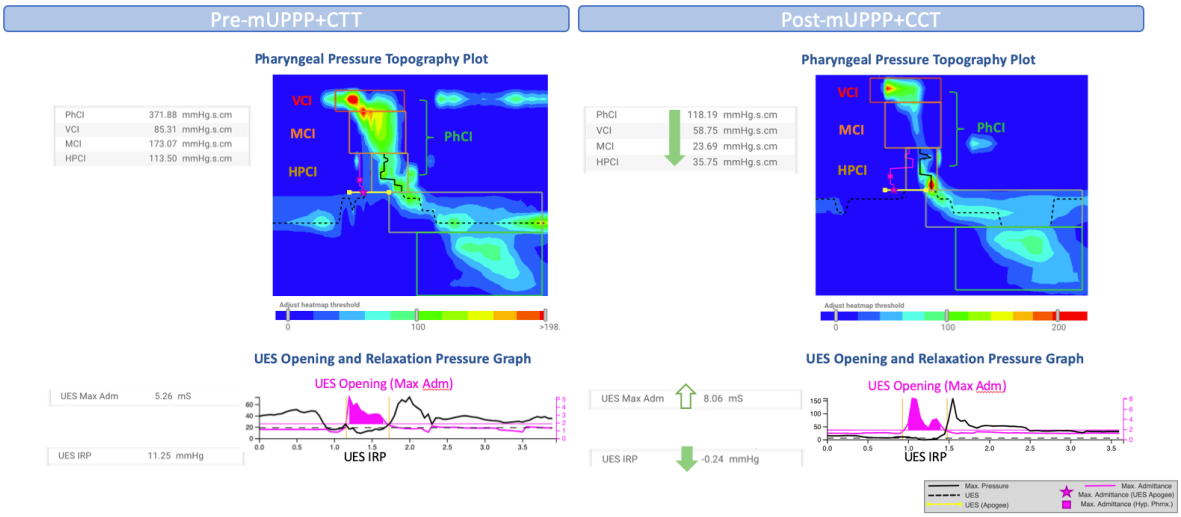

Figure 6-3 ONE PARTICIPANT EXAMPLE COMPARING A SINGLE SWALLOW OF 10 ML VOLUME OF THIN LIQUID PRE- AND POST-MUPPP+CCT.

On the left of the topography plots, the values of pharyngeal contractile integral (PhCI) along with the sub-components (velo-, meso- and hypo-pharyngeal contractile integrals) are shown, indicating a reduction of these values post-surgery in this participant. The UES opening and relaxation graphs along the bottom show an increase in the UES opening (measure by the UES Maximum admittance metric) and a reduction in UES relaxation pressure (UES IRP) following the surgery in this participant. When compared with the pre-surgery swallow, a reduction of the meso- and hypo-pharyngeal contractile pressures following surgery are evident, represented by cooler colours on the post-surgery topography plot.

UOS Relaxation and Opening Extent

UES relaxation pressure (UES IRP) was significantly reduced following mUPPP+CCT (P = 0.001,Table 6.2, Figure 6.4). Pairwise comparisons were significant for 5 and 10 mL volumes and thin (IDDSI 0) and thick (IDDSI 4) fluid consistencies ($p < 0.05$, Table 6.2). UES relaxation time (UES RT) and UES opening extent (UES Maximum Admittance) did not differ following the surgery (P = 0.192 and P = 0.67, respectively; Table 6.2).

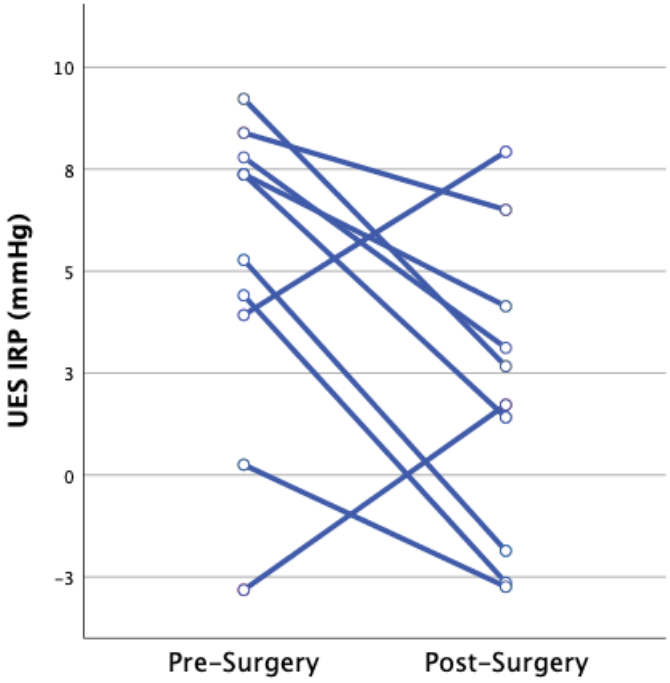

Figure 6-4 UES RELAXATION PRESSURES FOR EACH INDIVIDUAL PARTICIPANT PRE- AND POST-MUPPP+CCT SURGERY OF A 10ML THIN FLUIDS.

UES IRP was significantly reduced following mUPPP+CCT. In this graph, eight participants show a reduction of UES relaxation pressures following surgery, and two show an increase.

UES IRP: Upper Esophageal Sphincter Integrated Relaxation Pressure; mUPPP+CCT: Modified Uvulopalatopharyngoplasty and Coblation Channelling of the Tongue

P-HRM-I Additional Metrics

The Swallow Risk Index (SRI) was significantly reduced following surgery ($p = 0.01$, Table 6.2). Pairwise comparisons were significant for 20 mL volume and thick (IDDSI 4) fluid consistency ($p < 0.05$, Table 6.2). Bolus presence and timing measures (BPT and DCL) were unchanged following surgery. UES pre-swallow pressures (UES Basal Pressure; UES BP), UES post swallow pressures (UES Contractile Integral; UES CI), and the proximal esophageal contractile integral pressures (Prox Es CI) were unchanged following surgery (Table 6.2).

6.4 Discussion

This is the first study to prospectively evaluate swallowing using P-HRM-I technology pre- and post-mUPPP+CCT surgery for the management of moderate-severe OSA. The key biomechanical findings following mUPPP+CCT were: (1) pressures during velopharyngeal contraction were unchanged, (2) pressures during meso- and hypo-pharyngeal contraction were reduced and (3) pressures during UOS relaxation were reduced. The velopharyngeal findings suggest that the mUPPP surgery did not impair pressure generation at the velopharynx. The meso- and hypo-pharyngeal findings suggest that the CCT technique may reduce force generating capacity of these regions. Whilst reduced, it is notable that the pressures remained within normal limits. The reduction in UOS relaxation pressures may be an indirect result of reduced bolus propulsion due to reduced mesopharyngeal pressure generation, or represent improvement in UOS function. Participants overall did not report a change in dysphagia symptoms, suggesting that the biomechanical changes in swallowing following mUPPP+CCT were insufficient to clinically impact swallowing.

OSA severity and self-reported sleepiness tended to decrease following mUPPP+CCT surgery, however was not statistically significant likely due to the relatively small sample size for these outcomes. Significant reductions in these outcomes have previously been demonstrated (281). In addition, symptomatic dysphagia was unchanged post-surgery compared with pre-surgery. This is consistent with a previous study (310) and is an important finding, as dysphagia has previously been described as a post-operative complication of OSA (294, 295, 312, 313). However, those studies lacked pre-surgical assessment for comparison. Recent investigations have identified some people with OSA to have abnormal swallowing physiology without surgical treatment (247), consistent with our findings discussed in *Chapter 4*, irrespective of whether they self-reported symptoms of dysphagia (310, 682). This raises the possibility of poor perception of swallowing function in people with OSA which may be, at least in part, due to impaired pharyngeal sensation from OSA and/or pharyngeal surgery (270).

The mUPPP surgery is a reconstructive technique that involves a small degree of velar soft tissue resection but preserves the majority of the velum free edges (288). This has previously been hypothesized to impede pharyngeal driving pressures resulting in reduced pharyngeal constriction times seen on VFSS (290). In contrast, this P-HRM-I analysis demonstrates that velopharyngeal contractile pressures were unaffected following surgery. Thus, these results further indicate that the mUPPP technique does not impair pressure generation at the

velopharynx. Of note, whilst there was not a reduction in velopharyngeal pressures post-surgery, they did remain elevated when compared to published normative ranges (544) consistent with findings in *Chapter 5*. Furthermore, higher velopharyngeal contractile pressures associated with OSA have been previously reported, consistent with the findings in *Chapter 4*. Collectively, the elevated velopharyngeal contractile pressures are indicative of the underlying OSA pathophysiology (671), and not a consequence of the mUPPP+CCT surgery.

The tongue base plays a vital role during swallowing by generating the driving pressures behind the bolus (103, 119). The pressure gradient difference created by the elevation of the tongue base and the concurrent reduction in hypopharyngeal pressures results in efficient bolus clearance during swallowing (119) (*Refer to Section 1.1.3*). Although CCT applied to the posterior portion of the tongue is hypothesised to reduce volume and stiffen the tongue base (680, 683), a recent MRI study suggests there is no change in soft tissue volume, indicating this technique may merely stiffen the tongue base (679). It is plausible then that the CCT may cause a reduction in the swallow pressures at the meso- and hypo-pharyngeal regions. In this study, a reduction of the meso- and hypo-pharyngeal contractile pressures were demonstrated following the surgery. However, it should be acknowledged that they remained within normative ranges (544), starting at the upper-normal range pre-surgery and decreasing to the lower-normal range post-surgery. The long-term effect of these observed contractile pressure reductions superimposed with changes associated with the aging swallowing mechanism (663) are unknown.

A significant reduction of UOS relaxation pressures was observed following mUPPP+CCT, approaching the normative ranges (544). This is suggestive of a reduced degree of UOS restriction during swallowing (579) that could result from two differing processes. Firstly, the trend towards reduced intra-bolus distension pressures at the hypopharynx and increased UOS opening extent (measured by UES Maximum Admittance) following surgery, in addition to the decreased UOS relaxation pressures following mUPPP+CCT imply a beneficial effect of surgery in terms of the generation of a bolus-assistive pressure gradient. Collectively, these results extend the findings presented in *Chapters 4 and 5* suggesting UOS dysfunction is pre-existing in patients with moderate-severe OSA, rather than a consequence of the surgery. Additionally, swallowing improves following mUPPP+CCT, which may be representative of an improvement in OSA severity. Alternatively, the reduced mesopharyngeal and hypopharyngeal contractile pressures may lead to a diminished driving pressure behind the bolus during swallowing resulting in reduced bolus propulsion. In this context, the concurrent reduced UOS relaxation

pressures and meso- and hypopharyngeal contractile pressures could be a manifestation of impaired force generating capacity at the level of the tongue base region, which is the primary target of the CCT procedure. These hypotheses require further investigation in future studies.

The bolus flow timing measures of BPT and DCL were unchanged following surgery compared to pre-surgical baseline. When considered with the UOS biomechanical findings (UES IRP, UES Max Admit, UES RT), these results suggest that the mUPPP+CCT is associated with normal neuromodulation of the pharyngeal swallowing mechanism allowing for tailored motor output for adequate bolus accommodation (179, 667). In *Chapter 4*, we found that OSA participants had similar bolus flow timing measures to healthy controls. In *Chapter* 5, the post-mUPPP+/-CCT cohort had decreased bolus flow timing measures, and it was hypothesised that the surgery interfering with swallowing modulation. However, in this pre/post-surgery investigation, these measures did not change, demonstrate the surgery does not affect swallowing modulation.

The biomechanical findings from this interventional study, together with the unchanged patient-reported swallowing symptoms following surgery, may allay concerns regarding post-operative dysphagia being principally associated with mUPPP+CCT surgery. The findings support the results of VFSS based studies reporting minimal effects of OSA surgery on swallowing (290, 314), suggesting that the mUPPP+CCT technique may not be principally associated with impaired swallowing function, but may instead emphasise the pre-existing swallowing alterations in people with OSA (290, 314).

The following limitations of this study are acknowledged: (1) the number of participants involved in the pre- and post-surgical analysis was relatively small (n=10). Although it was sufficient to detect subtle changes to swallow function, a future investigation of a larger sample is needed to confirm these findings with respect to symptom outcomes; (2) although reflux symptoms were part of the exclusion criteria, a validated patient-reported outcome measure was not included. This may be a consideration in future studies as laryngopharyngeal reflux has been shown as an independent risk factor of dysphagia following upper airway surgery for OSA (287); and (3) the use of concurrent visual instrumental swallowing assessments, such as VFSS, was not used; this may support future clinical translation of the P-HRM-I findings.

6.5 Conclusion

This P-HRM-I study provides fundamental insights of the biomechanical pharyngeal swallowing outcomes following mUPPP+CCT surgery in a moderate-severe OSA cohort. Biomechanical alterations to swallowing following mUPPP+CCT were identified at distinct anatomical locations with potentially disparate effects on swallowing function. However, perceived dysphagia symptoms were unchanged following surgery, suggesting the alterations were insufficient to worsen self-reported swallowing. Further studies in larger cohorts are required to verify these novel findings.

The novel sub-clinical biomechanical swallowing outcomes reported in the OSA cohort and following mUPPP+/- CCT surgery in Chapters 4, 5 and 6 demonstrate the utility of the P-HRM-I technology. Valuable insight has been attained in these participant cohorts that expand the current understand of the underlying mechanisms contributing to alterations in swallowing, as well as the important evaluation of the effect of a contemporary surgical technique on swallowing outcomes. In the following Chapter, the P-HRM-I technology is applied to a different participant cohort, the critically ill following extubation or decannulation, to assess the swallowing biomechanics compared these to healthy controls. This participant cohort was chosen because the mechanisms that result in aspiration or altered swallowing function at the time of extubation or decannulation are seldom studied (346).

7. DYSPHAGIA ASSESSMENT IN THE CRITICALLY ILL FOLLOWING EXTUBATION OR DECANNULATION[3]

7.1 Introduction

There is increasing interest in the complications that occur after critical illness because these appear to play a major role in lengthening the duration of hospitalization (684, 685). However, post-extubation dysphagia (PED) remains inadequately identified (251, 637, 638). Nurse-conducted swallowing screening has previously been investigated (322, 637, 686, 687), however there are currently no recommendations to guide this practice (251) and variability in practice has been acknowledged (320, 336, 688, 689). Routine swallowing screening assessment of the critically ill following extubation is increasingly being recommended in the literature (349, 351, 690, 691). Furthermore, a core outcome measurement set for dysphagia interventions is currently being developed for adult patients in critical care (692).

The reported incidence of dysphagia in critically ill patients following extubation is 41% (250). Although resolution of aspiration occurs within 5 days following extubation (343, 693), dysphagia remains at hospital discharge in 40-60% of patients (321, 347, 349). Furthermore, self-reported dysphagia has been found in 23% of patients at 3-6 months following discharge (348). While the mechanisms leading to dysphagia in critically ill patients following extubation are considered multi-factorial, one recognised risk factor is the duration of endotracheal intubation (319, 323, 348). Prolonged ETI greater than 6 days has been associated with increased incidence and severity of dysphagia (320, 346, 348, 349).

Current knowledge of swallowing physiology in the critically ill population is not completely established (*Section 1.3.3*). Aspiration has typically been reported as a key outcome measure in critically ill patients following extubation (328-332), most likely due to the higher incidence of

[3] The data presented in this Chapter was **published**: Schar, M.S, Omari, T.I., Fraser, R.J., Bersten, A.D. & Bihari, S. (2021). Disordered swallowing associated with prolonged oral endotracheal intubation in critical illness. *Intensive Care Medicine*, *46* (1), 140-142 (*Appendix 3*). It was accepted for an **oral presentation** at Dysphagia Research Society Conference, San Diego, USA, March 2019; and for a **poster presentation** at the American Thoracic Society Conference, Dallas, USA, July 2019. This study was **awarded** the New Investigator Award by Dysphagia Research Society 2019. ($1,000, M.Schar); Higher Degree Research Student Publication Award, Flinders University, 2019. ($500; M.Schar) and the Hospital Research Foundation Travel Grant, 2019. ($3,500, M.Schar).

pneumonia following extubation in both medical and surgical cohorts (335, 694, 695). Few studies have investigated swallowing using instrumental swallow assessment; outcomes identified in these studies include: increased bolus time in the hypopharynx prior to swallow initiation (329, 330), incomplete epiglottic tilting (329), increased time of laryngeal closure, and shorter pharyngoesophageal segment opening (333). The majority of data regarding the presence of dysphagia following extubation is largely related to aspiration as the primary outcome measure (346), with minimal reference to mechanistic swallow function at the time of extubation (349) highlighting the need for further evaluation.

Aim

To utilise P-HRM-I to evaluate the pharyngeal biomechanics to objectively characterise swallowing in critically ill participants following extubation or decannulation and determine the effect of endotracheal intubation duration on swallowing.

7.2 Methods

Participants

The study was approved by the Southern Adelaide Human Research Ethics Committee (Protocol No. 202.15). The study was conducted between April 2016 and February 2018 in the Intensive & Critical Care Unit at Flinders Medical Centre. Inclusion criteria: critically ill patients who had endotracheal intubation or endotracheal intubation followed by tracheostomy with 48 hours or more of mechanical ventilation. At this institution, critically ill patients requiring prolonged intubation undergo a tracheostomy within 7-10 days of ETI. This early tracheostomy approach has been associated with improved health outcomes (696). Exclusion criteria: pre-existing or comorbid neurological diagnoses, head and neck or gastrointestinal surgery, previously diagnosed gastro-esophageal reflux disease, pregnancy, or elevated bleeding risk (INR >1.1). Informed consent or third-party written consent was obtained. The high resolution pharyngeal manometry control studies were obtained from an existing laboratory database of 68 healthy individuals from which cases were consecutively selected by age to match the patients.

Clinical Outcomes

Participant characteristics and relevant clinical data were collected at the time of the P-HRM-I study, including: age, gender and body mass index, hospital length of stay (LOS), duration of mechanical ventilation (MV), endotracheal tube (ETT) and tracheostomy tube (TT) type and size, sedation length and type, and alternative nutrition. Critical illness severity and comorbidity were assessed using the Acute Physiology and Chronic Health Evaluation III score (APACHE III)(697), Charlson Comorbidity Index (CCI) (698), Short Form Health Survey (SF-36) (699) and Clinical Frailty Scale (CFS) (700). Changed meal status was assessed by the 7-point Functional Oral Intake Scale (FOIS) (652).

PROMs of Swallowing

There were no PROMs of swallowing utilised in this study. The SSQ, which was used in *Chapters 4-6*, was validated in a primarily neurogenic cohort with a stable presentation of

dysphagia in an outpatient clinical setting (651). The SSQ was considered to be unsuitable PROMs instrument in the acute post-extubation setting.

P-HRM-I Swallow Assessment and Analysis

The P-HRM-I study was performed within 24 hours of extubation or tracheostomy decannulation. Whilst a standard protocol was followed, as described in *Section 3.4.3*, it should be noted that bolus preparation for this study was reflective of the procedures at the time (2016-2018). Participants were asked to swallow between 3-5 repeats of 5- and 10-mL volumes of thin (IDDSI 0) and extremely thick (IDDSI 4) liquids. The thin liquid bolus comprised of 0.9% saline and the extremely thick bolus at this time was the commercial standardized product of EFT Viscous Bolus (Sandhill Scientific, Denver USA). The control dataset was generated using the same bolus media.

Analysis of the P-HRM-I data occurred prior to the establishment of the standardised P-HRM-I Core and Additional Metrics (21). Consequently, four of the eight Core Metrics were not reported in this study. Whilst the PhCI was included, the sub-components of the VCI, MCI and HPCI were not.

Statistical Analysis

Statistical analysis was conducted as described in *Section 3.5*. Repeated measures variable data was analysed by using General Linear Modelling with the four bolus conditions as repeated measures and Group as a fixed factor: healthy controls versus critically ill participants, endotracheal intubation duration less than 7 days versus endotracheal intubation 7 days or more, and abnormal versus normal swallowing. Data were normalized by Log transformation and then analysed by using General Linear Modelling with bolus volume conditions (5/10ml) and consistency (thin/extremely thick fluids) as repeated measures with the Endotracheal Group (less than 7 days/ 7 days or more) as a fixed factor. Bonferroni adjustment was applied for multiple comparisons amongst the three groups. T-test or Kruskal-Wallis test were used for non-repeated measures for independent group comparisons. Proportionate data were compared by Fisher's exact test. Spearman correlations was used to examine relationships amongst

continuous variables. A statistically significant difference between participants and controls was defined with *P* values <0.05.

7.3 Results

Demographics

The healthy control group (n=24) had a mean age of 65 years (range 50-73), including 16 males and 8 females. In the critically ill following extubation or decannulation group, twenty participants were enrolled, however one participant was excluded due to a subsequent diagnosis of Guillain-Barré Syndrome, leaving a total of 19 participants. The reason for ICU admission for the remaining 19 participants include: cardiac (5), multi-trauma (2), respiratory (8) and surgical complications (4). Critically ill participant characteristics are presented in Table 7.1.

Table 7-1 CHARACTERISTICS AND CLINICAL DATA OF THE CRITICALLY ILL PARTICIPANTS AS AN OVERALL COHORT

Parameter	**Critically ill participants** (N=19)
Age, years	68 [64-72]
Gender, M:F	13:6
BMI	28 [25-31]
Hospital LOS, days	38 [27-49]
ICU LOS, days	23 [16-31]
Sedation, days	8 [5-11]
Endotracheal Intubation, days	8 [6-10]
Mechanical Ventilation, days	13 [7-19]
APACHE III Score	81 [68-93]
APACHE risk of death (%)	37 [22-52]
CCI	3.9 [3.1-4.8]
CCI %Survival@10y	54 [38-70]
SF-36	1081 [774-1387]
CFS	6.6 [6.1-7.1]
FOIS	3.6 [2.6-4.6]

The following parameters are shown: BMI (Body Mass Index), Hospital LOS (Hospital Length Of Stay), ICU LOS (Intensive Care Unit Length Of Stay), APACHE (Acute Physiology and Chronic Health Evaluation), CCI (Charlson Comorbidity Index), SF (Short Form Health Survey), CFS (Clinical Frailty Scale), and the FOIS (Functional Oral Intake Scale). Data expressed as mean [95% Confidence Intervals]. *indicates statistically significant difference based on Independent Samples T Test (*p<0.05, **p<0.005, ***p<0.0001).

P-HRM-I Core Metrics

Table 7.2 compares the P-HRM-I metrics for the critically ill participants following extubation or decannulation and the healthy controls, including post-hoc pairwise comparison between the critically ill sub-groups (ETI <7 days and ETI ≥7 days groups) and controls.

Table 7-2 P-HRM-I SWALLOW METRICS IN HEALTHY CONTROLS AND CRITICALLY ILL PARTICIPANTS

P-HRM-I Core Metrics Mean (95% CI)					
Metric	**Controls (n=24)**	**Critically ill participants (n=19)**	**P value**	**Sub-groups**	
				ETI <7 days (N=11)	**ETI ≥7 days (N=8)**
Pharyngeal Contractile Integral PhCI mmHg.cm.s	444 [359-529]	455 [360-550]	p 0.865	427 [301-553]	493 [345-641]
Hypopharyngeal Intra-Bolus Pressure IBP mmHg	10.5 [7.4-13.7]	13.1 [9.5-16.6]	p 0.287	12.6 [7.9-17.3]	13.7 [8.2-19.3]
[1]UES Integrated Relaxation Pressure UES IRP mmHg	4.8 [1.3-8.3]	11.6 [7.7-15.6]	**p <0.004***	8.9 [3.9-14.0]	15.3 [9.3-21.2][c]
UES Maximum Admittance UES Max Ad mS	6.0 [5.6-6.3]	4.4 [4.1-4.8]	**p<0.0001***	4.3 [3.8-4.8][c]	4.6 [4.0-5.1][c]

UES relaxation time **UES relax time** s	0.62 [0.58-0.66]	0.58 [0.53-0.62]	p 0.654	0.6 [0.6-0.7]	0.5 [0.5-0.6]
P-HRM-I Additional Metrics Mean (95% CI)					
[1]**Swallow Risk Index** SRI	2.8 [0-5.7]	7.3 [4.1-10.6]	**p <0.05***	8.8 [4.6-13.1] c0.07	5.2 [0.3-10.2]
[1]**Bolus Presence Time** **BPT** s	0.7 [0.5-0.9]	1.0 [0.8-1.2]	**p <0.05***	1.1 [0.8-1.3]	0.9 [0.6-1.2]
Peak Pharyngeal Pressure **Peak P** mmHg	241 [199-284]	201 [153-248]	p 0.764	178 [115-240]	232 [159-306]
Distension-Contraction Latency **DCL** s	0.5 [0.4-0.5]	0.4 [0.4-0.5]	p 0.247	0.5 [0.4-0.5]	0.4 [0.3-0.5]
[1]**UES basal pressure** mmHg	89.5 [71.3-107.7]	61.0 [40.5-81.42]	**p 0.015***	63.2 [36.1-90.4]	57.8 [71.1-107.9]

Data expressed as estimated marginal mean [95% Confidence Intervals]. Repeated measures ANOVA across bolus types with Group as Factor. 1data were normalised by Log transformation. *All critically ill participants different to healthy controls (*p<0.05, **p<0.01, ***p<0.001). ccritically ill participants sub-group based on ETI duration (<7 vs ≥7 days) different to Control with Bonferroni adjustment for multiple comparisons, p-values between 0.05-0.09 also shown in superscript.

UES IRP was significantly increased and UES max admittance was significantly decreased in the critically ill participants compared with healthy controls ($p<0.004$ and $p<0.0001$, respectively). During sub-group analysis, participants with an ETI ≥7 days showed an elevated UES IRP and both ETI <7 and ETI ≥7 showed a reduction in UES maximum admittance. There was no significant difference in UES relaxation time, IBP, or PhCI between the critically ill participants and healthy controls.

P-HRM-I Additional Metrics

The SRI was significantly higher in critically ill participants following extubation or decannulation compared to healthy controls across all tested bolus volumes and consistencies (Table 7.2; Figure 7.1A). As displayed in Figure 7.1B, two of the critically ill participants presented with an SRI >15 (predictive of aspiration) and a further six critically ill participants (and two healthy controls) had an elevated SRI indicating abnormal swallowing. Group comparison indicated a trending increase in SRI in the ETI ≥7 days group compared with the ETI <7 days group, however this did not reach significance.

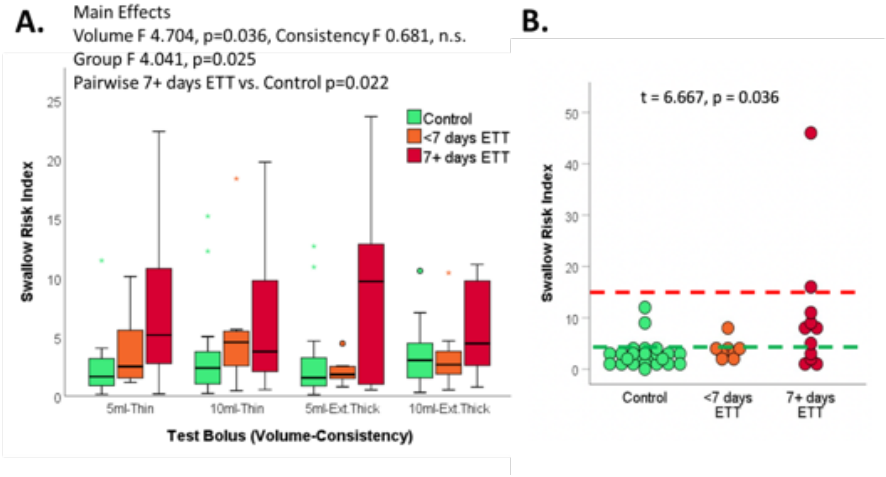

Figure 7-1 P-HRM-I-DERIVED SWALLOW RISK INDEX (SRI) SCORES IN THE HEALTHY CONTROL GROUP (GREEN) AND IN THE CRITICALLY ILL SUB-GROUPS OF ETI <7 DAYS (ORANGE) AND ETI ≥7 DAYS (RED).

A: Clustered boxplot of Swallow Risk Index by Volume (5/10 ml) & Consistency (thin/extremely thick fluids). B: Scatter plot of estimated marginal mean Swallow Risk Index for each participant. Horizontal green line indicates 90th percentile of controls as the threshold for normal swallowing. Horizontal red line corresponds to SRI>15, a level consistent with aspiration risk. Both participants with SRI>15 were referred for further fibreoptic endoscopic evaluation of swallowing investigation, which confirmed aspiration. t statistic and p-value shown for Independent samples Kruskal-Wallis test.

ETI: Endotracheal Intubation; P-HRM-I: Pharyngeal High-Resolution Manometry with Impedance; SRI: Swallow Risk Index

Compared with healthy controls, the critically ill participants had significantly reduced UES basal pressure and significantly longer BPT (Table 7.2; Figure 7.2).

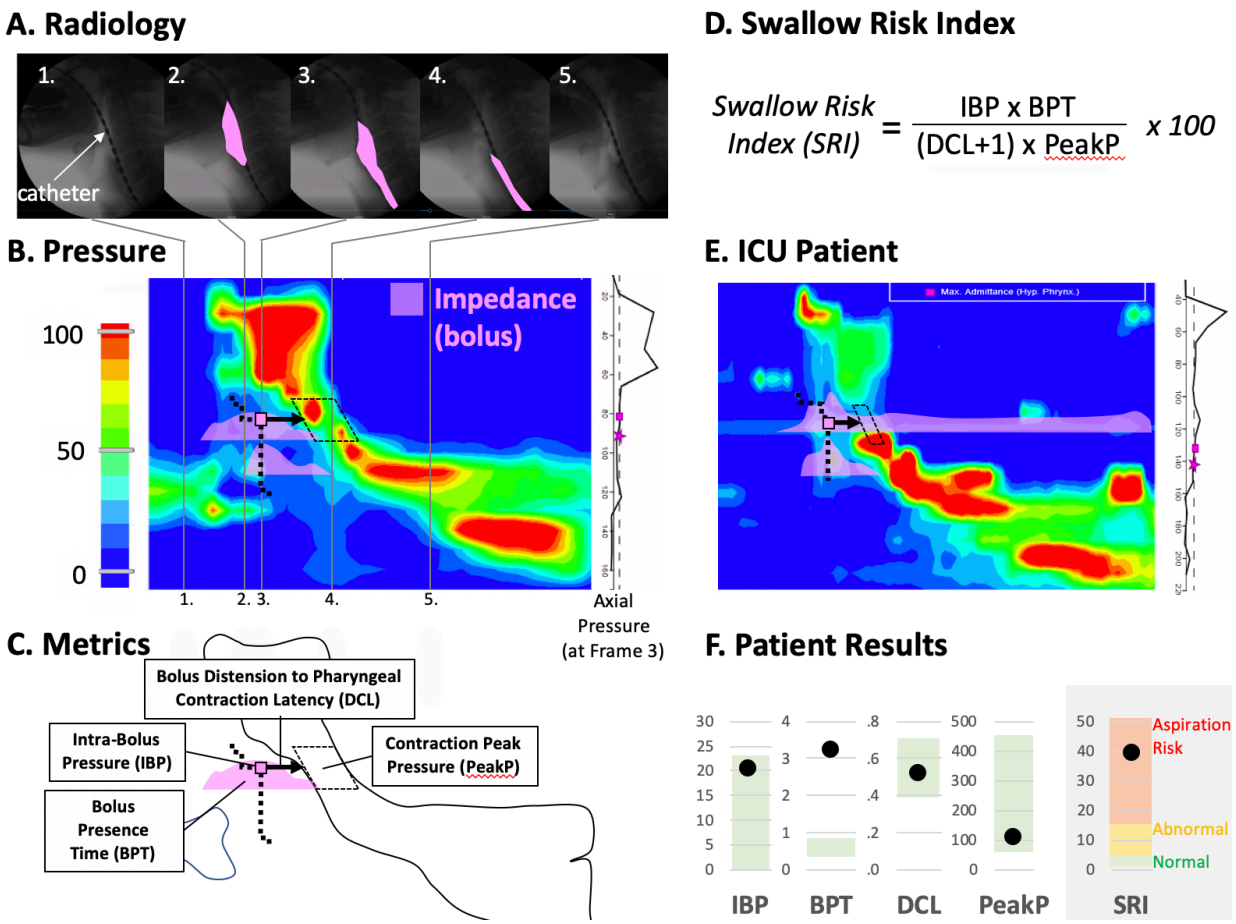

Figure 7-2 REPRESENTATION OF A NORMAL SWALLOW AND AN ABNORMAL SWALLOW, WITH ILLUSTRATION OF THE P-HRM-I DERIVED SWALLOW RISK INDEX (SRI) METRICS AND THE CONTRIBUTION OF THE BOLUS PRESENCE TIME (BPT) TO THE ABNORMAL SRI IN AN INDIVIDUAL CRITICALLY ILL PARTICIPANT.

B: A pressure topography of a healthy swallow. The impedance signal (shaded pink area) represents pharyngeal bolus presence. E: A pressure topography plot of a 10-ml liquid swallow in a critically ill participant (male, 77 years) after extubation. Compared to the healthy swallow in B, there is a prolonged bolus presence time (pink shading), representing an increased aspiration risk. F: Bar chart of the four key swallow metrics and SRI from the same swallow of the critically ill participant in E. An abnormal finding is indicated when the black dot lies outside of the green bar (normative range). Only BPT is abnormal, but IBP is at the upper limit and PeakP is at the lower limit of normal, therefore contributing to the overall increased SRI. The abnormal SRI was consistent with clinically observed aspiration using naso-endoscopic swallow assessment.

SRI: Swallow Risk Index; P-HRM-I: Pharyngeal High-Resolution Manometry with Impedance

Group comparisons demonstrated a trend for the DCL to be reduced in the ETI ≥7 days group (Figure 7.3A), and there was a highly significant correlation between endotracheal intubation duration and DCL overall (Figure 7.3B).

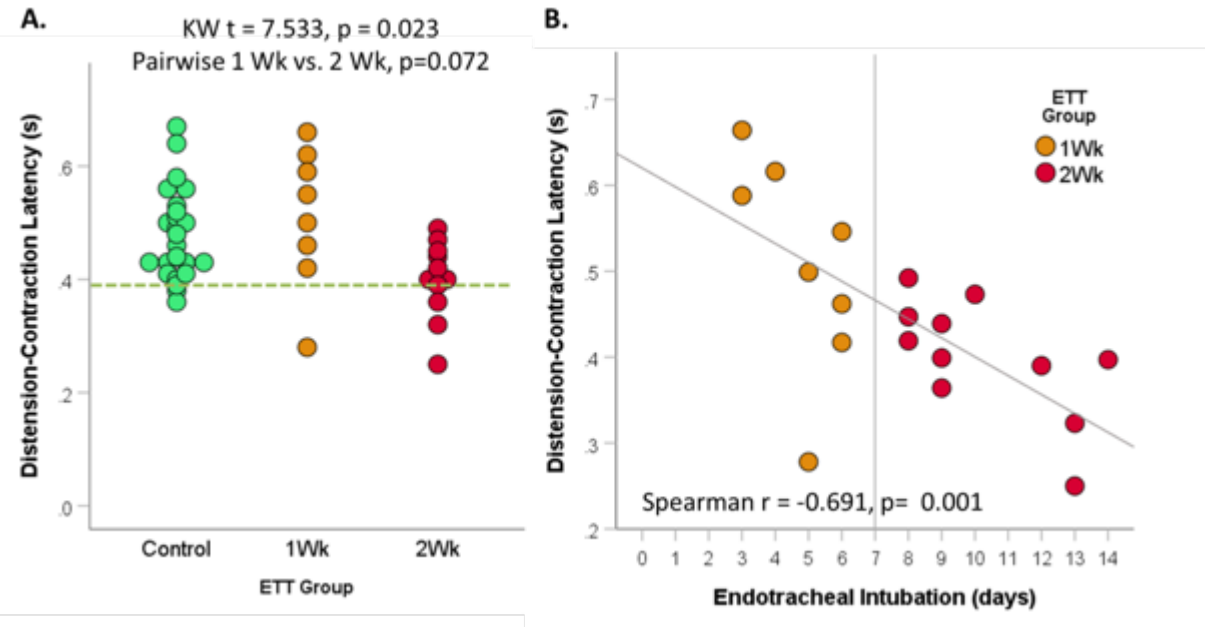

Figure 7-3 DISTENTION-CONTRACTION LATENCY (DCL) AND ENDOTRACHEAL INTUBATION DURATION. SCATTER PLOTS OF ESTIMATED MARGINAL MEAN DCL FOR PARTICIPANTS IN RELATION TO DURATION OF ENDOTRACHEAL INTUBATION.

A: Comparison of DCL of healthy controls (green) and critically ill participants with <7 days ETI (orange) and ≥7 days (red). Participants compared to controls, t statistic and p-value shown for Independent samples Kruskal-Wallis test and correlation based on Spearman rank test. B: Significant correlation shown with endotracheal intubation duration and DCL.

DCL: Distension-Contraction Latency

Clinical Outcomes

Of the 19 critically ill participants following extubation or decannulation, eight (42%) had abnormal swallowing determined by the SRI values (i.e. > the 90th percentile of the healthy controls) for at least two of the four test bolus combinations, comprising of seven participants in the ETI ≥7 days group and one participant in the ETI <7 days group. The following analyses explores the characteristics of those eight participants with abnormal swallowing compared to the 11 participants with normal swallowing.

Participants with abnormal swallowing had significantly longer ETI durations and significantly longer sedation times, as well as significantly increased overall hospital length of stay compared to participants with normal swallowing (Table 7.3). There was a strong correlation between duration of sedation and ETI duration (Spearman r = 0.726, p<0.001).

Table 7-3 PARTICIPANT CHARACTERISTICS AND CLINICAL OUTCOMES IN CRITICALLY ILL PARTICIPANTS WITH NORMAL AND ABNORMAL SWALLOWING

Clinical Outcomes	Critically Ill Participants		P value
	Normal swallow (N=11)	Abnormal swallow (N=8)	
Age, years	67 [63-73]	69 [62-76]	0.763
BMI, kg/m	29 [24-34]	27 [24-29]	0.470
Hospital LOS, days	29 [17-42]	50 [31-69]	**0.040***
ICU LOS, days	18 [10-27]	30 [15-45]	0.104
Sedation, days	5.7 [3.9-7.6]	12.0 [5.6-18.4]	**0.022***
Endotracheal Intubation, days	6.5 [4.5-8.4]	10.0 [7.5-12.5]	**0.019***
Mechanical Ventilation, days	9.7 [2.9-16.5]	17.2 [4.4-30.0]	0.214
APACHE III Score	74 [58-91]	88 [70-107]	0.258
APACHE III risk of death, %	30 [9-50]	46 [23-68]	0.278
CCI	3.5 [2.4-4.6]	4.5 [3.2-5.8]	0.251
CCI% Survival@10y	60 [42-79]	45 [12-79]	0.343
SF-36	1144 [829-1459]	906 [368-2180]	0.482
CFS	6.7 [6.2-7.2]	6.5 [5.2-7.8]	0.659
FOIS	3.7 [2.3-5.1]	3.5 [1.7-5.2]	0.819

Data expressed as mean [95% Confidence Intervals]. Abnormal swallowing defined by SRI > 90th percentile of Control Ranges for at least two of test bolus types. The following parameters are shown: BMI (Body Mass Index), Hospital LOS (Hospital Length Of Stay), ICU LOS (Intensive Care Unit Length Of Stay), APACHE (Acute Physiology and Chronic Health Evaluation), CCI (Charlson Comorbidity Index), SF-36 (Short Form Health Survey), CFS (Clinical Frailty Scale) and FOIS (Functional Oral Intake Scale). T-test , $p < 0.05$ statistically significant.

7.4 Discussion

This is the first study to use P-HRM-I to analyse swallowing biomechanics in a critically ill adult cohort following extubation. The key findings showed that 42% (8/19) of critically ill participants had features suggestive of abnormal swallowing within 24 hours of extubation or decannulation, and that this was significantly associated with ≥ 7 days of ETI, longer sedation duration and increased hospital length of stay. Key biomechanical alterations were observed in the critically ill participants compared with healthy controls, including: (1) altered UOS function, demonstrated by the concurrent increased UOS pressures, reduced UOS opening and reduced UOS basal pressures; and (2) altered bolus movement measures demonstrated by increased BPT.

The SRI in the critically ill following extubation or decannulation participants was significantly higher than in the age matched controls. Elevated SRIs above normative ranges were seen in 42% (8/19) of the critically ill participants, suggesting abnormalities of the swallow mechanism. A similar incidence of dysphagia in the critically ill following extubation (41%) was reported in the critically ill in a systematic review (250). However, it is difficult to compare our finding with the broader literature due to the heterogeneity of available studies, with variability in study designs, timing and type of swallow assessment, and characteristics of the cohorts studied (250, 251, 318). It is therefore unsurprising that a number of systematic reviews have acknowledged a wide range of reported incidence of dysphagia following extubation, from 3-63% (250, 251, 318), and 11-93% following tracheostomy decannulation (701). The current study detected a strong correlation between those critically ill participants who presented with dysphagia and an increase in hospital length of stay, which is consistent with previous publications (321-323). This is noteworthy considering the implications that increased hospital length of stay can have on health outcomes, cost, and resource requirements (319, 322, 686).

Two of the 19 critically ill participants had an SRI greater than 15, indicating dysphagia associated with probable aspiration (567). Importantly, these two participants did not demonstrate overt aspiration symptoms (i.e. silent aspiration) but following clinical FEES assessment, aspiration was confirmed. Visual instrumental assessment was not routinely conducted, however other studies utilising this method have reported silent aspiration in 20-56% of critically ill patients following extubation (338, 340, 341, 343). Silent aspiration could be related to reduced laryngeal sensation, which is one of the proposed mechanisms of post-extubation dysphagia (349-351). ETI has been associated with depressed laryngeal reflex, as well as reduced glottic opening (702). Studies also identified reduced cough strength, which was

associated with reduced glottic clearance, to be evident in critically ill patients following extubation (46, 320). These are clinically important observations given that aspiration of oropharyngeal secretions can cause considerable health complications, such as aspiration pneumonia (703).

Six of the critically ill participants had an SRI above the normative range, but below the aspiration threshold value of 15, indicating abnormalities of the swallow mechanism were identified. A plausible explanation of this finding could relate to functional compensation in the presence of reduced physiological reserve of the swallow mechanism. Adaptive swallowing strategies may occur during eating and drinking, thereby preventing aspiration. Such compensation has also been reported in age-related dysphagia (presbyphagia) (704). However, it is possible that these compensation mechanisms could be susceptible to becoming overwhelmed when further insults or clinical complications occur, which could accelerate the risk of aspiration (705). In addition to functional compensation, behavioural compensation may also occur, resulting in alterations to eating and drinking behaviours. This can negatively impact patients' overall oral intake, potentially leading to malnutrition and dehydration, which may result in delayed rehabilitation and increased hospital length of stay (243, 706-708).

An endotracheal intubation duration of 7 days or more was significantly correlated with dysphagia in the critically ill participants, suggestive that the mechanisms leading to post extubation dysphagia become more pronounced over time. The duration of ETI has previously been identified as a risk factor for post-extubation dysphagia (319, 323, 348) with prolonged ETI greater than 6 days is associated with increased incidence and severity of dysphagia (320, 346, 348, 349) but this is not always a consistent finding (338). The occurrence of dysphagia in critically ill patients following extubation is thought to involve a complex interplay between multi-factorial mechanisms (46, 349), including: (1) oropharyngeal and laryngeal injury directly associated with the endotracheal tube, (2) neuromyopathy resulting in neuromuscular weakness, (3) reduced laryngeal sensation, and (4) impaired cognition associated with sedation or delirium (46, 349).

P-HRM-I can identify subtle changes in swallow biomechanics that can assist in understanding the mechanisms contributing to PED in the critically ill, which could further assist in understanding the mechanisms contributing to post-extubation dysphagia (319, 323, 348). Four specific biomechanical parameters were different in the critically ill cohort when compared to age matched controls: (1) increased BPT, (2) increased UOS relaxation pressures (UES IRP),

(3) reduced UOS basal pressures (UES BP), and (4) reduced UOS opening (UES Max Admit), and are discussed below.

Critically ill participants demonstrated increased BPT compared to controls, representing longer bolus retention in the hypopharynx prior to UOS relaxation. These findings may be comparable with previous studies that reported delayed laryngeal closure and swallowing onset in critically ill patients post extubation (329, 330, 333). A possible underlying mechanism for this could relate to reduced oropharyngeal sensation following extubation. This abnormal biomechanical finding, when compared with healthy controls, may manifest as an increased latency between the bolus arrival in the hypopharynx and swallow initiation (44). This is a known feature of dysphagia often associated with neurogenic aetiologies and one that carries a higher risk of aspiration (709). A latency average of 7 seconds has been shown in critically ill patients at 24 hours following extubation (330), far exceeding the 2-3 seconds which is considered normal (73, 681).

Although the DCL was not significantly different in the critically ill cohort when compared with healthy controls, a significant association was observed with a shortened DCL and increased ETI duration. This metric indicates an altered bolus flow representative of a “late” propulsion of the bolus in the swallow sequence (closer to the hypo-pharyngeal contraction). This may be comparable with observations of a secondary or ‘pharyngeal’ swallow, which is initiated by direct pharyngeal stimulation without lingual propulsion and oral clearance and is considered an airway protection mechanism (710). This shortened DCL, along with increased BPT, together represent altered bolus movement patterns. Such patterns have previously been described in relation to the effects of sedation, analgesia and partial neuromuscular blockers (90, 612, 613). Whilst the bolus movement findings may reflect the ongoing effects of these medications, the medications may also contribute to impaired cognition. Both of these factors could be contributing mechanisms to swallowing impairment post extubation. Interestingly, in healthy participants, morphine and midazolam infusions have resulted in reduced bolus control, swallow frequency and airway protection (711).

Critically ill participants had reduced UOS basal pressures compared to controls. A number of mechanisms have been identified that alter UOS basal pressures, including sedation and analgesia (712). Thus, this finding may reflect the increase in sedation days required for increased endotracheal intubation duration. Interestingly, reduced UOS basal pressures have also been considered a non-specific feature of neurogenic swallowing dysfunction, being

recognised in patients diagnosed with motor neurone disease and associated with aging (154, 591).

Compared with healthy controls, UOS dysfunction was apparent in the critically ill cohort, determined by increased UOS pressures (UES IRP) and reduced UOS opening (UES Max Admit). However, there was no significant difference in UOS relaxation time. This is inconsistent with previous VFSS observations of reduced durations of pharyngoesophageal segment opening (333). This incongruous finding may reflect the limitation of VFSS to identify the timing of UOS relaxation compared with P-HRM-I. The features of elevated UOS relaxation pressures and reduced opening were examined and discussed in further detail in the OSA and post mUPPP+CCT cohorts (*Chapters 4 and 5)*.

The results in this study showed that the overall pharyngeal contractile pressures were not significantly different in the critically ill cohort compared with age matched controls. This was unexpected given one of the proposed mechanisms of dysphagia in the critically ill following extubation is neuromuscular weakness (349-351). Acquired generalised muscle weakness occurs in 25-50% of patients who undergo ETI (713, 714), and oropharyngeal skeletal muscle degeneration due to disuse has been hypothesised (715). In previous studies, tongue strength following extubation has been examined. Using the Iowa Oral Performance Instrument, maximum tongue strength was significantly reduced in critically ill patients following extubation when compared with healthy controls (716), and following ETI of 7 days or more (328). It should be acknowledged that these findings are measures of the maximum tongue pressure at the *anterior and posterior dorsal surface*, which are distinct from the P-HRM-I metrics that provides data of *tongue base* pressures during swallowing. Future studies may consider evaluating the maximum generated pressures of the anterior tongue, using the IOPI, as well as the tongue base pressures, using P-HRM-I, in critically ill patients following extubation.

There are acknowledged limitations to this study. Firstly, it involved a heterogeneous cohort (admitted to ICU for assorted clinical causes including acute respiratory disease), however the participants enrolled were representative of typical non-neurological critically ill patients treated in a tertiary hospital. Secondly, the study was conducted prior to the standardised P-HRM-I metrics (21) and therefore the sub-pharyngeal contractile integrals were not included in the analysis. Thirdly, longitudinal data was not collected, therefore it was not established if changes in swallowing were temporary or permanent. This should be considered for future studies given that self-reported symptomatic dysphagia is reported to persist at 6 months post hospital

discharge (348). Finally, dysphagia was assessed using P-HRM-I only, and the addition of visual instrumental swallow assessment may provide additional data to aid dysphagia interpretation in this critically ill population (717). However, it is recognised that VFSS is not suitable for application in the critical care setting (330, 331, 334) and a parallel invasive swallow assessment may have been too challenging for this population.

Future studies should consider conducting P-HRM-I and FEES swallowing assessments by the bedside with a restricted bolus administration protocol to identify swallowing patterns that contribute to the manifestation of dysphagia in this population and correlate biomechanical findings with visual instrumental observations. Larger cohorts of critically ill patients with longitudinal study designs are required to establish associations with meaningful clinical outcomes, including pneumonia rates and hospital length of stay, as well as to identify the key mechanisms that cause dysphagia in this population. This type of research may inform clinical guideline development regarding validated clinical indicators for those critically ill patients who would most benefit from timely swallowing assessment and intervention.

7.5 Conclusion

Global abnormality in swallowing was common in critically ill participants following extubation or decannulation and was associated with prolonged intubation, as well as longer sedation duration, and increased hospital length of stay. P-HRM-I assessment identified altered UOS function and altered bolus movement measures in critically ill participants compared to controls, revealing novel biomechanical alterations in the swallowing mechanism in this population. Further research is required with larger participant enrolment to confirm these findings and determine correlations with meaningful clinical outcomes.

In Chapter 7, P-HRM-I measures revealed novel biomechanical metrics that characterised dysphagia in the critically ill following extubation or decannulation. Another patient cohort where dysphagia is commonly reported is following HNC treatment. In the following Chapter, swallowing biomechanics are investigated using simultaneous P-HRM-I and VFSS in a post-HNC treatment cohort with moderately-severe dysphagia.

8. ASSESSMENT OF DYSPHAGIA FOLLOWING HEAD AND NECK CANCER TREATMENT[4]

8.1 Introduction

Swallowing assessment is common practice following treatment for HNC (366, 718) due to the high prevalence of post-treatment dysphagia (252). Acute and long-term dysphagia is a recognised complication following treatment for HNC, which is negatively associated with health-related quality of life (378)(*Section 1.3.4*). VFSS has primarily been used to characterise pathophysiological oropharyngeal swallowing changes following HNC treatment, with identified abnormalities including base of tongue dysfunction, reduced laryngeal elevation, reduced pharyngeal contraction, impaired epiglottic movement and reduced UOS opening (366, 380-388).

Altered bolus flow outcomes of pharyngeal residue and penetration/aspiration have been identified in VFSS and FEES studies following HNC treatment. For example, a recent systematic review reported the frequency of pharyngeal residue at 12 months post-treatment to be 73.8%, and continue to increase over time (366). Pharyngeal residue has been associated with poor pharyngeal constriction on VFSS (385). The review also noted an increased frequency of aspiration and penetration from 16.2% at 6 months to 33.6% at 12 months post-treatment (366). Incomplete or delayed laryngeal vestibule closure was identified to contribute to risk of penetration/aspiration (385).

P-HRM with or without impedance is considered by The European Society for Swallowing Disorders White Paper to have potential for identifying the pathophysiological mechanisms contributing to dysphagia in patients with HNC at the time of diagnosis and following treatment (719). Three studies have utilised P-HRM-I to assess swallowing post HNC treatment. However, two studies only investigated the validity and reliability of metrics, such as hypopharyngeal IBP (561) and the swallow risk index (572), without reporting the additional P-HRM-I metrics. The most recent publication by Schaen-Heacock and colleagues (2020) compared the pharyngeal pressures metrics of patients with sub-acute- and chronic-radiation-associated dysphagia (28). They found that both cohorts presented with reduced velopharyngeal pressure maximum and

[4] The data detailed in this Chapter was presented as a **poster** at the Australian and New Zealand Head and Neck Cancer Society, Virtual Conference, Queenstown, New Zealand. August 2021.

duration, hypopharyngeal maximum and pharyngeal pressure duration and contractile integral. The authors recommended that future studies should examine the relationship of reduced pressures and durations with efficiency of bolus propulsion and risk of penetration/aspiration (28).

Existing P-HRM-I studies have not completely characterised swallowing function following HNC treatment. Therefore, more comprehensive evaluation of the swallowing biomechanical measures in this population is required, and together with VFSS assessment may provide greater understanding of the contributing mechanisms to the dysphagia pathophysiology following HNC treatment.

Aim

To use P-HRM-I to assess the swallowing biomechanics in participants with HNC who undergo multi-modality treatment and correlate these metrics with VFSS measures.

8.2 Methods

Participants

Ethical approval was granted by the Southern Adelaide Clinical Human Research Ethics Committee (No. 283.11). Data was collated from patients following HNC treatment who had been referred for a videomanometry swallow assessment on clinical grounds between January 2016 - September 2019 (conducted by M.Schar). All participants had provided written informed consent for use of their research studies. Demographics, diagnosis, staging and treatment data were collected from medical record review.

PROM of Swallowing

The Functional Oral Intake Scale (FOIS) (652) was used to assess oral intake status. The FOIS has recently been shown to be significantly correlated with patient reports of swallowing difficulty following HNC treatment (720, 721).

Videomanometry Swallowing Assessment

The videomanometry swallowing assessment protocol was followed (*Section 3.4.3*). Cessation of testing of a fluid viscosity (thickness level) and/or amount (5 or 10 mL) occurred if aspiration and/or significant residue was observed during the assessment. The VFSS recording were analysed using quantitative measures of residue and aspiration, including: (1) the validated Dynamic Imaging Grade of Swallowing Toxicity (DIGEST)(482), with aspiration (Safety Grade), residue (Efficiency Grade), and dysphagia severity (Summary Grade) (482); (2) the penetration-aspiration score (PAS), which was used to grade penetration and aspiration (455); and (3) the normalised residue ratio score (NRRS), which was used to quantify vallecular and pyriform sinus residue (483) of thin liquid swallows.

The standard P-HRM-I analysis protocol was used (*Section 3.4.3*). Data of the thin liquid swallows of 5 mL volumes were collated. Additional analysis to categorise multiple swallowing behaviour (MSB) was conducted based on a recently published study from our group characterising this phenomenon in healthy adults (722). MSB was defined by a sequence of two

or more swallows with an inter-swallow interval of ≤ 5 seconds. Further sub-typing of MSB was defined as: (1) secondary dry, the bolus is completely transferred through the pharynx in one swallow followed by one or more dry swallows; (2) preceding dry, the bolus is completely transferred through the pharynx in one swallow attempt preceded by one or more dry swallows; (3) piecemeal, the bolus is transferred through the pharynx distributed through two or more swallows; and (4) clearing, the bolus is incompletely transferred through the pharynx with evidence of bolus residue between swallows (722).

The mean values for each of the swallow function metrics were determined for 5 mL thin liquids due to these being the only consistent tested bolus volume and consistency that was tested in all of the fourteen participants. Proportionate data were compared by Fisher's exact test. Spearman correlations was used to examine relationships amongst continuous variable. Refer to *Section 3.5* for details of the statistical analysis.

8.3 Results

Participants

Fourteen participants (13 males, 1 female; with an average age of 63 years, ranging 48-74 years) were enrolled in this study. Table 8.1 displays the participant characteristics. Twelve participants (86%) had oropharyngeal cancer; one participant had nasopharyngeal cancer; and one participant had laryngeal cancer. Staging data was available for 12 participants; 67% (8/12) were diagnosed with advanced HNC (stages III and IV). There was missing staging data for two of the participants as they were not recorded in the medical records. All participants underwent multi-modality treatment; 100% (14/14) had radiotherapy; 57% (8/14) had concurrent chemoradiation; 36% (5/14) had surgery followed by chemoradiation; and one participant had surgery followed by radiation. The median duration since treatment was 11 months [IQR 6, 39 months]. At the time of dysphagia assessment, 64% (9/14) required alternative nutrition via an enteric feeding tube (FOIS Grade 1-3 with nil or minimal oral intake).

Table 8-1 PARTICIPANT CHARACTERISTICS

Participants	Gender	Age	Primary tumour site	Subsite	Stage	Treatment	Duration since HNC treatment (months)	FOIS Grade
1	M	58	Oropharynx	Tonsil, soft palate	IV	Sx, CRtx	5	2
2	M	71	Oropharynx	Tonsil	II	CRtx	84	5
3	M	71	Nasopharynx	-	u/k	CRtx	64	2
4	M	65	Oropharynx	Tongue base	u/k	Sx, CRtx	126	5
5	M	57	Oropharynx	Tonsil	II	CRtx	11	4
6	M	48	Oropharynx Oral cavity	Tongue base Floor of mouth	I II	Sx CRtx	30	2
7	M	48	Oropharynx	Retromolar trigone	IV	Sx, CRtx	7	3
8	M	74	Oropharynx	unknown	IV	CRtx	29	2
9	M	57	Oropharynx	Tongue base	IV	CRtx	6	2
10	M	65	Oropharynx	Tonsil	II	Sx, Rtx	6	6
11	F	64	Oropharynx	Hypopharyngeal	III	CRtx	18	5
12	M	74	Larynx	Supraglottic	III	CRtx	5	2
13	M	63	Oropharynx	Tonsil	IV	CRtx	4	3

14	M	62	Oropharynx	Tonsil	IV	Sx, CRtx	10	2

CRtx: Chemoradiation; Sx: Surgical Tumour Resection; Rtx: Radiotherapy; FOIS: Functional Oral Intake Scale; u/k: unknown

Swallow Assessments

Simultaneous videomanometry data was available for nine of the 14 participants. The remaining five participants underwent separate VFSS and P-HRM-I investigations within 1-2 months. Only data from the 5 mL thin liquid was analysed due to this being the only consistent tested bolus volume and viscosity for all participants. These results are reflective of the degree of dysphagia apparent in this post HNC treatment cohort whereby the swallow protocol was truncated due to observed aspiration.

VFSS Measures

All participants underwent VFSS, enabling derivation of PAS, NRRS and DIGEST scores (Table 8.2). 93% (13/14) of participants had a DIGEST Summary Grade of 1-4, representing a dysphagia severity range between mild to life-threatening, with a median Grade of 2 representing moderate dysphagia [IQR 1-3]. One participant had a DIGEST Summary Grade of 0, representing no dysphagia. 86% of participants (12/14) demonstrated penetration and/or aspiration. The median PAS was 6 [2, 7], indicating aspiration; 10 participants had a PAS ≥5, indicating silent penetration or aspiration; two had a PAS of 2-4, indicating penetration; and two had a PAS of 1, indicating no penetration or aspiration

Table 8-2 VFSS OUTCOMES WITH P-HRM-I-DERIVED SRI AND MSB

Participants	VFSS-derived Measures						P-HRM-I-derived Measures	
	Penetration-Aspiration Scale	Valleculae Residue (NRRSv)	Pyriform Residue (NRRSp)	DIGEST Grade			Dominant Swallow Pattern	SRI
				Safety	Efficiency	Summary		
1	2	**1.08**	0	0	**3**	**2**	**MSB - Piecemeal**	**45**
2	**5**	**0.06**	**0.62**	1	**3**	**2**	**MSB - Piecemeal**	**19**
3	**6**	**0.1**	**0.09**	**2**	**3**	**3**	Single	**62**
4	**7**	**0.91**	**1.26**	**3**	**4**	**4**	**MSB - Clearing**	**35**
5	1	0	0	0	1	0	Single	3
6	**8**	**0.08**	**0.95**	**2**	**3**	**3**	**MSB - Clearing**	**47**
7	**5**	**1.19**	**0.55**	1	**3**	**2**	MSB - Secondary	1
8	**8**	**0.06**	**0.09**	**2**	1	**2**	Single	4
9	**6**	-	-	**2**	**3**	**3**	MSB - Secondary	**20**
10	1	**0.22**	0	0	**2**	1	Single	4
11	2	0	0	0	1	1	Single	2
12	**8**	**0.42**	**0.6**	**2**	**3**	**3**	Single	7
13	**6**	**0.34**	0	1	1	1	Single	1
14	**7**	**0.14**	0.02	**2**	**3**	**3**	**MSB - Piecemeal**	**59**

VFSS: Videofluoroscopy Swallow Study; PAS: Penetration-Aspiration Scale: 1=none, 2-5= penetration, 6-8= aspiration; NRRS: Normalised Residue Ratio Scale (v, valleculae, p, pyriform sinus); DIGEST: Dynamic Imaging Grade of Swallowing Toxicity (safety, efficiency and grade); MSB: Multiple Swallowing Behaviour with Subtype: secondary dry, piecemeal and clearing; SRI: Swallow Risk Index value. Bold values represent abnormal values.

To determine how the VFSS measures related to each other and to aid in the interpretation of the swallowing studies, a correlation analysis was performed (Table 8.3). Participants who presented with silent penetration or aspiration (PAS ≥5) were more likely to demonstrate abnormal DIGEST Grades compared to those who did not (Safety: 2 [1, 2] vs 0 [0, 0], MWU test t=2.994, p<0.005; Efficiency: 1.5 [0.25, 2.75] vs 3 [2.5, 3], ns; Severity 3 [2, 3] vs 1 [0.25, 1.75], MWU test t=2.426, p<0.05). Participants who presented with silent penetration to the level of the true vocal folds or aspiration (PAS ≥5) exhibited a significantly higher degree of pyriform sinus residue (NRRSp 0.55 [0.05, 0.79] vs 0 [0, 0], MWU test t=2.543, p<0.05) but not of vallecula residue (NRRSv 0.34 vs 0.11, ns).

Table 8-3 CORRELATION OF VFSS OUTCOMES

	Maximum Penetration-Aspiration Score (DIGEST Safety)		**Maximum % of pharyngeal residue (DIGEST Efficiency)**		**Dysphagia Severity (Summary DIGEST Grade)**		**Valleculae Residue (NRRSv >0.02)**		**Pyriform Sinus Residue (NRRSp >0.02)**	
	r	*p* value	*r*	*p* value	*r*	*p* value	*r*	*p* value	*r*	*p* value
Aspiration (PAS ≥ 5)	**0.878**	**0.000****	0.343	0.231	**0.724**	**0.003****	0.116	0.706	**0.666***	**0.013**
Valleculae Residue (NRRSv >0.02)	0.182	0.551	**0.568**	**0.43***	0.371	0.231	-	-	0.175	0.568
Pyriform Sinus Residue (NRRSp >0.02)	**0.773**	**0.002****	**0.718**	**0.006****	**0.779**	**<0.002****	0.539	0.57	-	-

Spearman rho Bold values correspond to significant correlations at p <0.05* or <0.01**.

P-HRM-I Measures

P-HRM-I derived SRI values with dominant swallow pattern and SRI values for individual participants are presented in Table 8.2. Five participants (36%) demonstrated abnormal MSB: three participants displayed piecemeal, and two participants displayed clearing sub-type behaviours.

The median SRI was 16 [3, 45], which exceeded the established 95th percentile of healthy controls (SRI >4), suggesting abnormal swallowing. Seven participants (50%) had an SRI (>15), which is indicative of aspiration risk (569). The participants who presented with an abnormal MSB (piecemeal or clearing sub-type) with a 5 mL thin liquid were more likely to present with an increased SRI (SRI 45 [27, 53] vs 4 [1, 17], MWU test t = 39, p < 0.05), indicative of abnormal swallowing function with increased aspiration risk.

The correlation analysis of VFSS outcomes with SRI and MSB is presented in Table 8.4. Although the SRI (>15) demonstrated a sensitivity and specificity (ROC area under the curve 0.725) that was predictive of silent penetration and aspiration (PAS ≥5), it was not significantly correlated with PAS. However, an increased SRI (>15) was significantly correlated with increased DIGEST Efficiency and Summary Grades (Refer Figure 8.1).

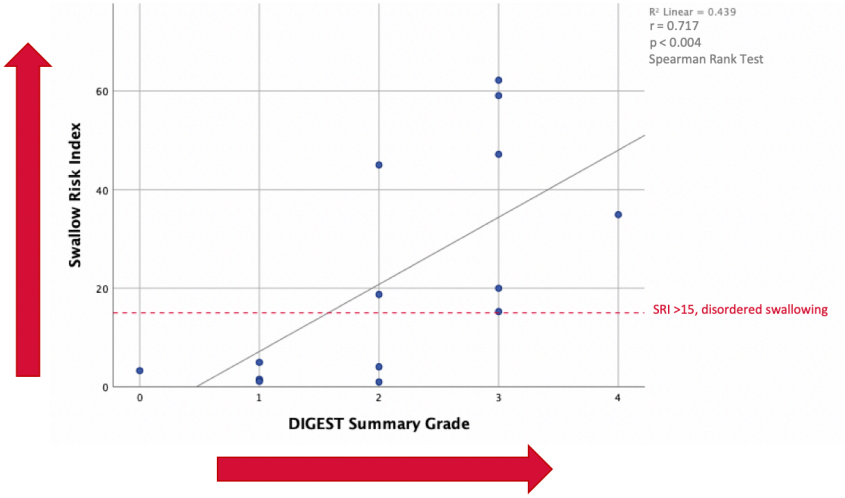

Figure 8-1 P-HRM-I DERIVED SWALLOW RISK INDEX CORRELATED WITH INCREASED VFSS DERIVED DIGEST DYSPHAGIA SEVERITY.

Table 8-4 CORRELATIONS OF P-HRM-I DERIVED INCREASED SWALLOW RISK INDEX (SRI) AND NUMBER OF MULTIPLE SWALLOWING BEHAVIOUR (MSB) WITH VFSS MEASURES

	VFSS Outcomes											
	PAS		NRRSv		NRRSp		DIGEST Safety		DIGEST Efficacy		Summary DIGEST Grade	
	r	*p* value	*r*	*p* value	*r*	*p* value	*r*	*p* value	*r*	*p* value	*r*	*p* value
Increased SRI	0.354	0.214	0.022	0.943	0.345	0.248	0.505	0.066	**0.642**	**0.013***	**0.717**	**0.004****
Increased MSB	0.141	0.063	0.337	0.260	0.030	0.319	0.235	0.419	**0.597**	**0.024***	0.442	0.113

Spearman rho Bold values correspond to significant correlations at p <0.05* or <0.01.**

Swallow Risk Index

The SRI is a composite score comprising of four individual P-HRM-I measures: peak pharyngeal pressure (PeakP), intra-bolus pressure (IBP), bolus presence time (BPT), and distension to contraction latency (DCL) (Section 3.4.3.3). The graphs below in Figure 8.2 illustrate the contribution of the individual P-HRM-I metrics when SRI <15 and >15. Although a short DCL and prolonged BPT were the two metrics that predominantly contributed to abnormal SRI values, these were not statistically significant on an individual basis.

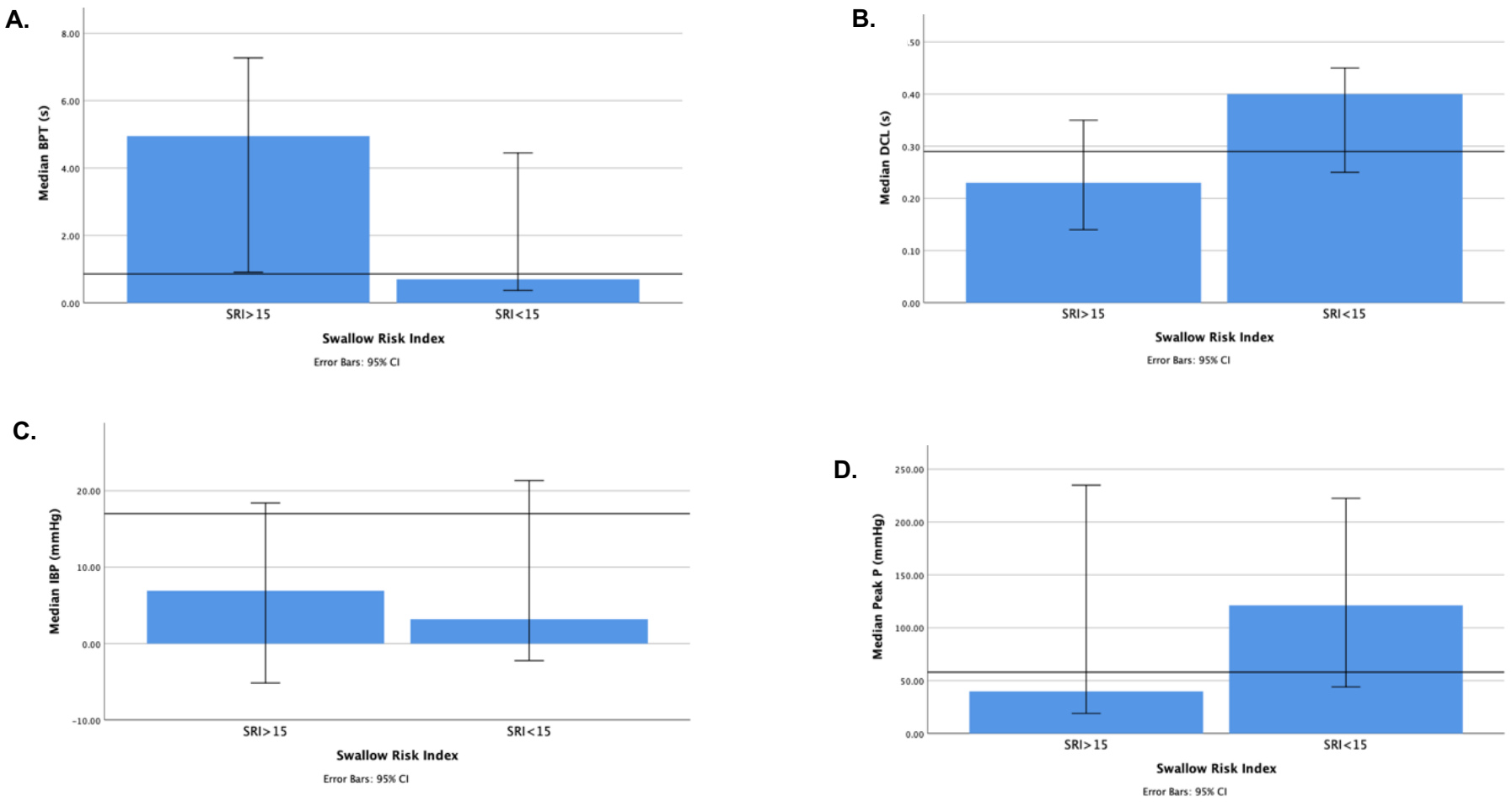

Figure 8-2 GRAPHS SHOW CONTRIBUTION OF INDIVIDUAL METRICS TO THE SWALLOW RISK INDEX (SRI).

A. Bolus Presence Time (BPT), B. Distension-Contraction Latency (DCL), C. Intra-Bolus Pressure (IBP), and D. Peak Pharyngeal Pressure (peak p) and are shown with their contribution with normal (<15) and abnormal (>15) SRI. 5th CI are shown on Peak P and DCL and 95Th CI are shown on DCL and IBP.

The correlations between specific SRI metrics and VFSS measures are presented in Table 8.5, Figure 8.3 and Figure 8.4. Shortened DCL was significantly correlated with: (1) increased maximum percentage of pharyngeal residue, as measured by DIGEST Efficiency, (2) pyriform residue, as measured by the NRRSp, and (3) increased severity of pharyngeal dysphagia (DIGEST Summary Grade). Prolonged BPT was significantly correlated with maximum percentage of pharyngeal residue (DIGEST Efficiency). Shortened DCL and prolonged BPT were not significantly associated with premature spillage. However, Peak P was significantly associated with premature spillage.

Table 8-5 CORRELATIONS OF SRI-P-HRM-I METRICS WITH VFSS OUTCOMES

SRI Metrics	VFSS Outcomes													
	PAS		Valleculae Residue (NRRSv 0.02)		Pyriform Residue (NRRSp 0.02)		DIGEST Safety		DIGEST Efficiency		Summary DIGEST Grade		Premature Spillage	
	r	*p* value	*r*	*p* value	*r*	*p* value	*r*	*p* value	*r*	*p* value	*r*	*p* value	*r*	*P value*
Peak P *mmHg*	-0.270	0.351	-0.041	0.898	-0.195	0.523	-0.093	0.752	-0.175	0.549	-0.178	0.542	**0.617**	**0.25***
BPT *s*	0.118	0.688	0.198	0.516	0.427	0.145	0.233	0.423	**0.706**	**0.005****	0.498	0.70	0.278	0.358
DCL *s*	-0.232	0.426	-0.342	0.253	**-0.577**	**0.39***	-0.496	0.72	**-0.718**	**0.004****	**-0.592**	**0.026***	0.283	0.327
IBP *mmHg*	-0.172	0.558	-0.102	0.742	-0.376	0.205	-0.121	0.680	-0.084	0.776	0.009	0.975	-0.178	0.561

Spearman rho Bold values correspond to significant correlations at p <0.05* or <0.01.**

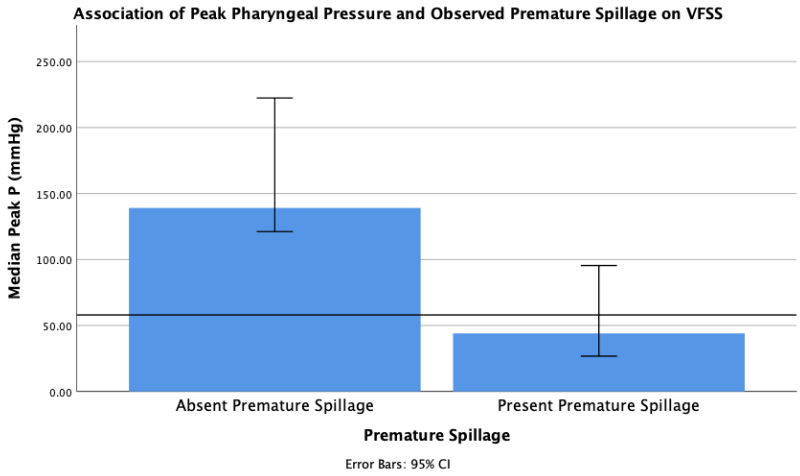

Figure 8-3 THE ASSOCIATION OF PEAK PHARYNGEAL PRESSURE (PEAK P) AND PREMATURE SPILLAGE ON VFSS.

Peak P was significantly associated with premature spillage

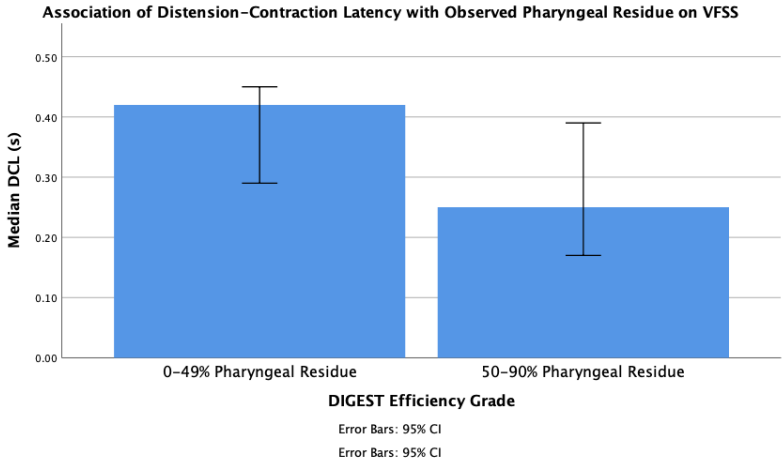

Figure 8-4 THE ASSOCIATION OF DISTENSION-CONTRACTION LATENCY (DCL) WITH OBSERVED PHARYNGEAL RESIDUE ON VFSS.

Shortened DCL was significantly associated with increased pharyngeal residue.

P-HRM-I Core Metrics

Eight (57%) participants showed evidence of pharyngeal weakness based on reduced pharyngeal contractility integrals compared to the 5th percentile of normative ranges for 5 mL thin liquids (Figure 8.5A). Of these, four participants showed an abnormal MCI reduction and one participant an abnormal VCI reduction in isolation. Concurrent abnormal reduction in more

than one anatomical region was observed in three participants, with two showing concurrent reduction in both velo- and mesopharyngeal contractile pressure and one participant showing reductions across velo-, meso- and hypo-pharyngeal contractile pressures (VCI, MCI, and HPCI, respectively). Six (43%) participants showed evidence of UOS dysfunction (venn diagram Figure 8.5B) evidenced by two or more altered UOS metrics of elevated IRP, elevated IBP, reduced opening and/or reduced relaxation time. Only two (14%) participants presented with concurrent pharyngeal weakness and UOS dysfunction.

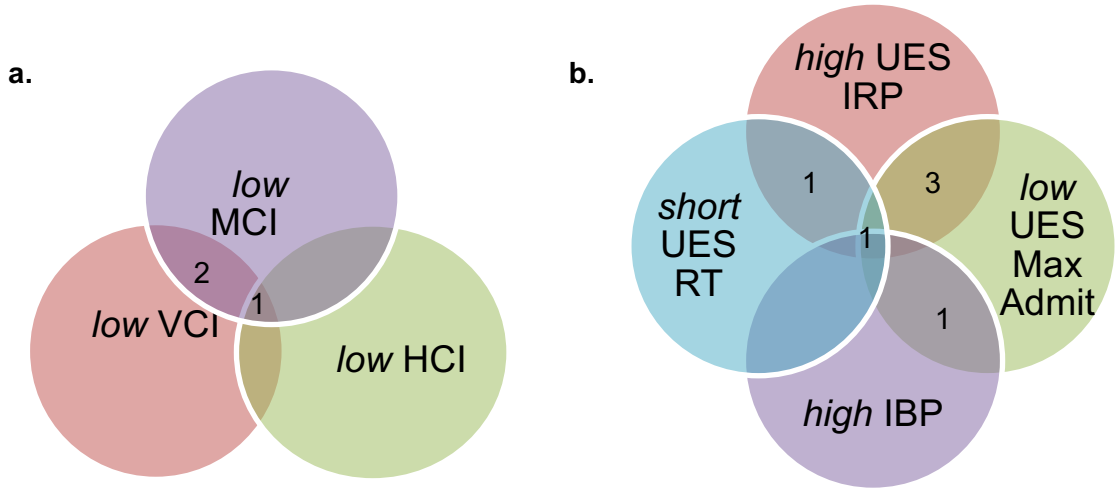

Figure 8-5 P-HRM-I CORE METRICS OF THE POST HNC TREATMENT COHORT.

A: Individual reduced pharyngeal contractility integrals are shown: VCI, Velopharyngeal Contractility Integral, MCI, Mesopharyngeal Contractility Integral and HCI, Hypopharyngeal Contractility Integral. Reduced MCI was evident in seven participants, with three demonstrating additional reduced VCI and/or HCI. B: UOS Function measures: six post-HNC treatment participants presented with UOS dysfunction as evidenced by two or more altered UOS metrics of elevated UES IRP, integrated relaxation pressure, elevated IBP, intra-bolus pressure, reduced UES opening, UES maximum admittance, and/or reduced UES RT, relaxation time.

The correlations between the P-HRM-I Core metrics and VFSS Outcomes are presented in Table 8.6. In summary, pharyngeal contractility metrics were not significantly correlate with VFSS Outcomes. Increased UES relaxation pressure (IRP) was significantly associated with increased DIGEST Safety and Summary Grades and demonstrated a trend towards significance with increased PAS. In addition, reduced UES maximum opening (admittance) was significantly associated with increased DIGEST Safety Grades and also demonstrated a trend towards significance with increased PAS. Prolonged UES relaxation time was significantly correlated with increased DIGEST Efficiency and Summary Grades.

Table 8-6 CORRELATIONS BETWEEN P-HRM-I CORE METRICS AND VFSS OUTCOMES

P-HRM-I Core Metrics	VFSS Outcomes											
	PAS		Valleculae Residue (NRRSv 0.02)		Pyriform Residue (NRRSp 0.02)		DIGEST Safety		DIGEST Efficiency		DIGEST Grade	
	r	*p* value	*r*	*p* value	*r*	*p* value	*r*	*p* value	*r*	*p* value	*r*	*p* value
PhCI mmHg.cm.s	-0.076	0.797	-0.099	0.747	-0.119	0.699	0.033	0.912	-0.229	0.430	-0.110	0.709
VCI mmHg.cm.s	0.151	0.605	0.113	0.713	0.178	0.560	0.214	0.462	0.010	0.973	0.105	0.721
MCI mmHg.cm.s	-0.002	*0.994*	-0.306	0.310	-0.232	0.446	0.021	0.943	-0.447	0.109	-0.203	0.486
HPCI mmHg.cm.s	-0.234	0.421	0.179	0.558	-0.119	0.699	-0.035	0.906	-0.012	0.967	-0.053	0.858
IBP mmHg	-0.172	0.558	-0.102	0.742	-0.376	0.205	-0.121	0.680	-0.084	0.776	0.009	0.975
UES IRP mmHg	0.530	0.051	0.047	0.879	0.450	0.123	**0.600**	**0.023** *	0.378	0.183	**0.605**	**0.022** *
UES Max Ad mS	-0.492	0.074	-0.033	0.915	-0.393	0.184	**-0.533**	**0.050** *	-0.308	0.283	-0.471	0.089
UES relax time s	0.025	0.934	0.435	0.137	0.192	0.529	0.279	0.334	**0.698**	**0.005****	**0.585**	**0.028** *
UES BP mmHg	-0.245	0.399	0.58	0.851	0.158	0.605	0.163	0.578	0.489	0.076	0.299	0.299
UESCI mmHg.cm.s	-0.183	0.532	0.152	0.621	0.25	0.934	-0.007	0.981	0.338	0.237	0.139	0.635
UES Peak P mmHg	-0.096	*0.745*	0.091	0.768	0.181	0.554	0.021	0.943	0.111	0.706	0.039	0.895
ProxEsCI mmHg.cm.s	0.069	0.815	-0.259	0.393	-0.122	0.692	0.030	0.918	-0.005	0.987	0.094	0.750

Bold values denote statistical significance * Denotes p < 0.05; ** denotes p <0.01

Reduced mesopharyngeal contractility was significantly associated with abnormal multiple swallowing behaviour (141 [32, 217] vs 16 [1, 56], MWU test t = 5, p <0.05) (Figure 8.6).

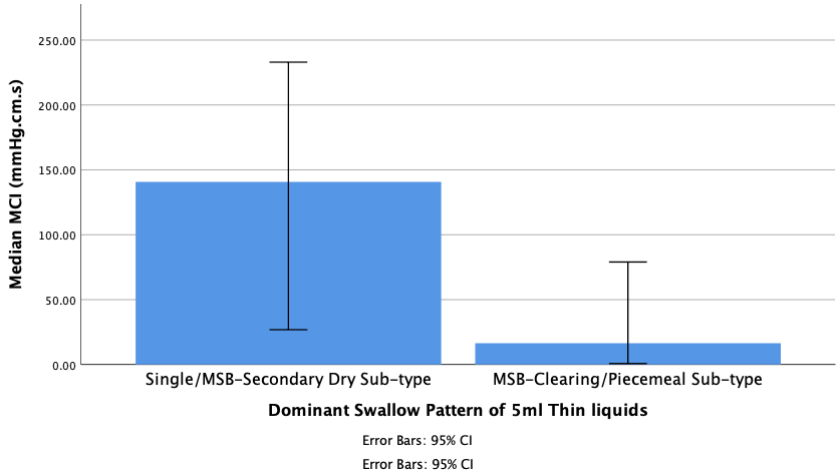

Figure 8-6 THE CONTRIBUTION OF MESOPHARYNGEAL CONTRACTILITY (MCI) AND MULTIPLE SWALLOWING BEHAVIOUR (MSB).

A reduction in MCI was significantly associated with abnormal MSB (Clearing/Piecemeal Sub-types).

P-HRM-I Additional Metrics

Measures of UOS basal pressure (UES BP) and contractility (UES CI and UES Peak P) did not correlate with VFSS measures, with only a trend of higher UOS basal pressure with DIGEST Efficiency Grades notable (Table 8.6).

8.4 Discussion

This study provides new insights into the range of biomechanical alterations in swallowing following HNC treatment and demonstrates that the application of P-HRM-I technology with VFSS provides a complementary understanding of the pathophysiology of dysphagia in this cohort. A high prevalence of disordered swallowing was found in participants following multi-modality HNC treatment, mostly with advanced oropharyngeal cancer. VFSS findings demonstrated that: (1) 93% of participants presented with disordered swallowing, and (2) 86% were observed to have laryngeal penetration and/or aspiration. Further discussion of the VFSS outcomes of aspiration and residue in comparison to the literature are outlined in *Appendix 4*. P-HRM-I findings revealed that: (1) 50% of participants presented with an SRI indicative of aspiration risk that was largely driven by altered bolus timing metrics, and correlated with residue on VFSS, (2) swallows characterised with abnormal MSB of piecemeal and clearing sub-types had abnormal SRI (>15), (3) 57% of participants presented with reduced pharyngeal contractile pressures and 43% presented with UOS dysfunction, and (4) altered UOS metrics were significantly associated with increased aspiration and residue.

The median SRI of the post-HNC treatment cohort was 16, but surprisingly, abnormal SRIs (>15) did not correlate with higher PAS scores. This is in contrast to previous studies, which demonstrated strong correlation of abnormal SRIs with observed aspiration on VFSS in heterogenous populations or larger sample size (567, 574) as well as in a post-HNC treatment population (572). In contrast, abnormal SRI (>15) did correlate with increased DIGEST Safety Grades, which modifies the PAS to account for amount and frequency of aspiration (482). Additionally, an abnormal SRI (>15) also correlated with the DIGEST Efficiency and Summary Grades. Thus, the SRI showed significant correlations with the VFSS-derived bolus safety and efficiency functional outcomes. It should be acknowledged that whilst the acquisition rate of 15 fps of the VFSS images are considered sub-optimal with current international consensus, the validity of the PAS has been shown not to be compromised with 15 fps compared with the optimal 30 fps rate (478).

Prolonged BPT and shortened DCL were identified as the main contributory biomechanical measures associated with abnormal SRI values in this study cohort. These impedance-based timing metrics have not previously been reported following HNC treatment. Prolonged BPT and shortened DCL are suggestive of poor oral lingual control identified by premature spillage on VFSS (497, 581), which has been reported in patients following HNC treatment (723-725).

Prolonged BPT may be comparable to VFSS findings in these studies, including delayed swallow initiation, prolonged latency from hyoid burst and laryngeal vestibule closure and/or uncoordinated timing of bolus propulsion (382, 385, 726). These parameters have been associated with increased airway penetration and/or aspiration across various populations (385, 727, 728). Shortened DCL during liquid swallowing is considered a correlate of impaired oro-lingual control evidenced by pre-swallow bolus presence on VFSS, which is hypothesized to represent ineffective pressure generation behind the bolus. This pressure generation is primarily due to late-phase propulsion of the hypo-pharyngeal contractile pressure, rather than the timely (early) propulsive pressure of the tongue base (497, 581). These abnormal flow timing metrics may indicate altered peripheral sensory afferent function of the pharyngeal swallowing mechanism (497), which may be associated with the primary tumour and/or the oncologic treatment (726, 729). However, in our study, a significant correlation between these P-HRM-I metrics and VFSS evidence of premature spillage was not found. This inconsistency between P-HRM-I equivalent altered bolus metrics with VFSS observations may reflect the limitations of VFSS derived binary measure of premature bolus spillage (e.g. present vs absent) and further support the need for a quantified VFSS-derived validated measure, such as from the Dynamic Swallow Study (DSS) (730), to provide more accurate interpretation.

Abnormal MSB, with a piecemeal or clearing sub-type, was observed in 36% of the post-HNC treatment cohort. Additionally, participants with abnormal MSB were more likely to present with a higher SRI. The relationship between MSB and aspiration is not entirely established. Furthermore, the mechanisms involving pharyngeal residue, the number of swallows required to clear the residue, and penetration/aspiration are unclear (731, 732). However, a moderate correlation between pharyngeal residue severity, the efficiency of residue clearing, and penetration and aspiration was reported using FEES (733). Furthermore, the risk of penetration/aspiration was increased during clearing swallows with pre-swallow residue, up to 4.6 fold greater with thin liquids (734). Interestingly, a recently published P-HRM-I-based study in a healthy adult population found that MSB occurred more frequently with larger bolus volumes, and were largely characterised by secondary dry swallows as opposed to clearing, piecemeal or preceding dry swallows (722). In comparison, over one third of the post-HNC treatment cohort in our study had abnormal MSB with piecemeal or clearing subtype with a small volume, thereby suggesting a higher aspiration risk in these participants. Additionally, reduced tongue base contractile pressures, as measured by the MCI, was significantly associated with abnormal MSB. This is unsurprising, given that tongue base contraction behind

the bolus, as well as pharyngeal shortening and elevation of the UOS during bolus transit, and sequential pharyngeal contraction are all mechanisms that assist with pharyngeal clearance (5, 667).

Pharyngeal weakness was demonstrated in 57% of the post-HNC treatment cohort. This was determined by reduced pharyngeal contractile integrals, of which reduced MCI were most frequently observed. This finding of pharyngeal weakness is consistent with the literature. A systematic review examining swallowing abnormalities in post-HNC treatment patients found a high prevalence of tongue base dysfunction and reduced pharyngeal contraction (380). These have been associated with pharyngeal residue on VFSS (372, 383, 385, 735, 736) and reduced pharyngeal pressures on low-resolution manometry (387). Recently, reduced tongue volume (measured on CT) has been identified following chemoradiation for HNC treatment (647). This may be a contributory mechanism leading to reduced pharyngeal pressure generation, and may also play a role in reduced tongue base contractile pressures, as seen in our post-HNC treatment cohort. Another potential mechanism contributing to reduced pharyngeal pressures could be increased pharyngeal lumen size resulting from muscle atrophy (370), which has been associated with radiation-induced fibrosis following HNC treatment (375). A recent P-HRM-I study examining dysphagia following radiation therapy found decreased pharyngeal pressure and duration to be significant in the velopharynx only, and not in the mesopharynx, hypopharynx or UOS (28). While reduced pharyngeal contractile pressures were identified on P-HRM-I in our study, they were not associated with pharyngeal residue on VFSS. Knigge and Thibeault (2016) reported a similar finding in their concurrent VFSS and HPRM study, which could suggest that efficacious vallecula clearance is influenced by multiple factors additional to the tongue base driving pressures (107). Pharyngeal residue may therefore be a complex inter-play between the driving pressures of the tongue base, the subsequent pharyngeal stripping wave, and the UOS relaxation and opening extent (105, 737). The assessment in our study was conducted only with 5 mL thin liquids. Increased bolus volumes have demonstrated greater differences in pharyngeal contractile values (544), thus, a greater discrepancy may have been demonstrated with higher bolus volumes compared with the healthy control ranges.

Altered UOS function was observed in 43% of participants following HNC treatment, determined by two or more abnormal UOS metrics on P-HRM-I. UOS dysfunction is a recognised complication following chemoradiation treatment for HNC (384, 738, 739). The post-HNC treatment cohort in our study presented with a median duration of 11 months post-HNC treatment, which is consistent with chronic radiation injuries (370, 371). The effects of chronic

radiation injury on muscles can include increased fibrotic tissue replacing the muscle fibres, loss of vascularity, and loss of matrix organisation leading to muscular and peripheral neurological attenuation (370) (*Section 1.3.4*). Reduced UOS opening and duration of opening has been observed during VFSS in patients post-HNC radiation treatment (382, 383, 386, 740). VFSS-derived assessment of UOS stricture, however, has shown poor reliability (741). The recommended P-HRM-I-derived criteria for UOS stricture comprise of the concurrent presentation of UES IRP >9 mmHg and IBP >18. Interestingly, none of the participants in our study met these criteria, indicating that UOS stricture did not characterise the observed dysphagia. This is unsurprising in a small cohort with recruitment bias as described earlier, particularly given that the prevalence of UOS stricture is only 7% following chemoradiation treatment for HNC (254).

UOS dysfunction derived from P-HRM-I measures was significantly associated with abnormal DIGEST Efficiency and Safety Grades on VFSS. These findings demonstrate that the degree of UOS relaxation and opening provides an integral contributory function for efficacious bolus flow (105, 737). Reduced bolus efficiency resulting in post-swallow pharyngeal residue has been shown to be associated with reduced pharyngeal propulsion and contractile vigor (382, 383)(Kotz et al., 2004), as well as impaired UOS relaxation and duration (585, 742). In our study, reduced UOS relaxation time was significantly associated with increased pharyngeal residue and severity of dysphagia, which has been previously reported (740). However, prolonged UOS relaxation duration has previously been found to be significantly associated with aspiration, albeit in a predominantly heterogenous neurological cohort with dysphagia (567, 709). These contrasting findings demonstrate the ability of the altered UOS metric to dichotomise findings with consideration of the aetiology. Contemplating the underlying physiology, prolonged UOS relaxation time may be an indication of altered modulation of the central pattern generator (179), whereas shortened UOS relaxation time could reflect peripheral impairment, resulting from causes such as radiation associated injury (386). Additionally, reduced UOS opening, measured by UES Max Admittance, and increased UOS pressure were significantly associated with increased DIGEST Safety grade. A reduced UES Max Admit measure is considered a non-specific marker of pharyngeal function, which is influenced by multiple factors(591), including structural pathology (e.g. cricopharyngeal bar), reduced distention associated with weak tongue base propulsion and /or weak pharyngeal contraction, and piecemeal swallowing resulting in reduced volume swallowed per swallow (591). Given no structural abnormalities were observed during the VFSSs by the radiologist, the measures of

reduced UOS opening are most likely representative of the high percentage of MSB associated with reduced mesopharyngeal contractile pressures.

Over a decade ago, pharyngeal manometry was recognised as an assessment method that could complement visual instrumental swallowing assessments in the HNC cohort (387). Their preliminary findings using low-resolution manometry technology demonstrated the potential relationship with VFSS. In our current study, clear significant associations have been demonstrated using high-resolution technology with concurrent pressure-impedance data and validated VFSS functional outcomes. Furthermore, the application of P-HRM-I in post-HNC treatment participants to optimize assessment and management has been recently recommended by an international dysphagia association (719). These factors support future hypothesis driven research in the application of this translational P-HRM-I technology in post-HNC treatment cohorts to potentially identify key biomechanical impairment patterns. This small data set demonstrates that UOS dysfunction, as opposed to reduced pharyngeal pressures, are present with a significant relationship with observed dysfunction on VFSS. Future studies should expand these preliminary findings.

There are several recognised limitations of this study. These include: (1) This study was an analysis of clinically acquired HNC P-HRM-I and VFSS swallow assessment and therefore the HNC location, staging, and treatment differed within the cohort. Given that the oropharynx is the leading anatomical site for HNCSCC in a younger cohort (743), analysis of a homogenous group following concurrent chemoradiation treatment is recommended in future studies; (2) the sample size was small (n=14); (3) simultaneous collection of patient-reported outcome measures of swallowing did not occur, which was reported as a critical outcome measure in this particular cohort (400); (4) the VFSS 15 fps frame rate may have prevented identification of the maximum aspiration and residue scores limiting the VFSS and P-HRM-I correlation; and (5) unavailable data that may have affected swallowing outcomes, including the presence of trismus (744), neck dysfunction (745), oesophageal pathology, (746), OSA/sleep disturbances (747, 748), sarcopenia (749) was unavailable. Future studies should include quantitative measures of VFSS metrics, such as the Dynamic Swallow Study (DSS) (122, 750), with concurrent functional measures of residue and aspiration and ascertain the strength of the associations with P-HRM-I-derived metrics in larger cohorts. The novel results in this study demonstrate the utility of P-HRM-I with VFSS to characterise the underlying mechanisms contributing to dysphagia at an individual patient level. This is important for guiding /informing interventions/exercises to target improved swallowing in these high-aspiration risk patients.

Future study protocols may consider evaluating prophylactic swallowing exercise programs that up until now have shown inconsistent treatment effects (751).

8.5 Conclusion

P-HRM-I assessment of swallowing in a post-HNC treatment cohort presenting with moderate to severe pharyngeal dysphagia and a high prevalence of aspiration identified two distinct altered biomechanical patterns: (1) reduced pharyngeal contractile pressures and (2) UOS dysfunction. Observed pharyngeal residue and aspiration on VFSS were associated with altered UOS dysfunction measures, however not with reduced pharyngeal contractile pressures. This study demonstrates that concurrent P-HRM-I and VFSS studies may provide critical thresholds to enhance the interpretation of VFSS observations. Future studies should consider correlating P-HRM-I metrics with quantified VFSS measures.

In Chapter 8, it was demonstrated that the application of P-HRM-I technology can operate with VFSS to improve understanding of the pathophysiology of dysphagia following HNC treatment. Altered biomechanical patterns of reduced pharyngeal contractile pressures and UOS dysfunction were observed in the post-HNC treatment cohort. A novel procedure targeting dysphagia following HNC treatment is tongue base augmentation. The biomechanical impact of this procedure on swallowing has not been evaluated. In the following Chapter, P-HRM-I technology is utilised as an intervention outcome measure to determine the effect of this novel tongue base augmentation procedure for the management of moderate-severe dysphagia following HNC treatment.

9. DYSPHAGIA ASSESSMENT PRE-AND POST-TONGUE-BASE AUGMENTATION IN PARTICIPANTS FOLLOWING HEAD AND NECK CANCER TREATMENT WITH MODERATE TO SEVERE DYSPHAGIA[5]

9.1 Introduction

Cancer survivorship and health-related quality-of-life (HRQOL) are integral components of cancer treatment and surveillance (361). HRQOL following HNC treatment relates to the perceived impact of the treatment sequalae on a patient's QOL. A wide range of diminished physical, emotional, functional and social aspects of HRQOL have been reported in HNC survivors following treatment (361, 752, 753). Given the 20% increase in incidence of the younger population (<65 years) who are living longer with the HNC treatment sequalae (743, 754), HRQOL following HNC treatment is now considered a critical element of care.

Dysphagia has been identified as a strong predictor of reduced HRQOL for up to 10 years post-HNC treatment (378, 639, 640). Changes in eating habits and reduced food intake occurs in up to 40% of patients following treatment (641), while 3-10% of patients require percutaneous endoscopic gastrostomy (PEG) for nutritional support at 12 months or more after HNC treatment (642, 643). Additionally, changes in eating habits and feeding tube use have been associated with reduced ability to return-to-work (755, 756). Each of these factors have been associated with reduced QOL (757-760). Accordingly, there has been considerable research targeting improvements in swallowing outcomes following HNC treatment. The initiation of swallowing exercises prior to treatment is one strategy aimed at maximising swallowing muscle strength and range of movement pre-treatment to optimise swallowing outcomes after treatment (644). However, the efficacy of pre-treatment (prophylactic) swallowing exercises is unclear, with inconsistent treatment effects being demonstrated (645).

[5] The data presented in this Chapter was an accepted for an **oral presentation** at the Australian and New Zealand Head and Neck Cancer Society Conference, Adelaide in November 2019. This study was **awarded** the Australian and New Zealand Head and Neck Cancer Society, Research Foundation Board Grant, 2018. ($10, 000, CI M.Schar) and College of Medicine and Public Health, Flinders University: Higher Degree Research Grant, 2019. ($4000; CI M.Schar), which supported data collection and analysis. It has been **submitted for publication** to *Head and Neck* in December 2021: Schar, M., Woods, C., Omari, T., Footner, L., Marshall, N., Doeltgen, S., Cock, C., Thompson, A, Nguyen, T., Athanasiadis, T. & Ooi, E. Pharyngeal tongue base Augmentation for Dysphagia (PAD): A prospective case series in patients post Head and Neck Cancer (HNC) Treatment (*Appendix 3*).

Lipofilling injections using adipose tissue, also known as fat grafting, is an established surgical technique in reconstructive plastic surgery, with novel application in the management of dysphagia following HNC treatment (648, 649, 761-763). Lipofilling injections aim to improve swallowing function by augmenting pharyngeal or laryngeal structures. Although adipose tissue is considered an ideal permanent filler due to the biocompatible and autologous properties that provide for optimal amalgamation into the host tissue site (763), use of a temporary filler, such as hyaluronic acid (HA) with biodegradable properties (764), may be a suitable alternative while establishing the efficacy and safety profile of the procedure.

Tongue base dysfunction is recognised as a contributory mechanism of dysphagia following HNC treatment as measured by VFSS. In particular, reduced tongue base and pharyngeal wall muscle volume has been associated with reduced pharyngeal constriction and increased pharyngeal residue (646). Augmentation of the tongue base aims to target the key anatomical sites that contribute to tongue base dysfunction (380, 647) and has been reported to result in improved swallowing outcomes (648, 649). In a case series, Kraaijenga and colleagues (2016) found that four of the six post-HNC treatment patients demonstrated a reduction of penetration/aspiration following tongue base injection, with two of the patients no longer requiring alternative nutrition via a feeding tube (649). It has been hypothesized that this procedure artificially augments the mesopharyngeal volume and, as a biomechanical consequence, increases the force generation capacity during swallowing. However, evaluation of swallowing biomechanics before and after the procedure has not occurred. The primary hypothesis of this study was that tongue base augmentation increases mesopharyngeal wall volume/thickness, measured using magnetic resonance imaging (MRI), and improves mesopharyngeal force generation measured by P-HRM-I. A secondary hypothesis was that when compared to pre-procedure status, a reduction of post-swallow pharyngeal residue and improved patient-reported dysphagia symptom scores would be seen following the procedure.

Aim

To evaluate the effect of tongue base augmentation in participants with dysphagia following HNC treatment on swallowing outcomes using P-HRM-I biomechanical data, videofluoroscopy swallowing study (VFSS), and self-reported symptoms of dysphagia.

9.2 Methods

Participants

Ethical approval (No. 39.17) was granted by the Southern Adelaide Clinical Human Research Ethics Committee. Participants were prospectively enrolled and provided written consent between January 2018 - September 2019.

Participants were recruited through the Otolaryngology Head and Neck Surgery Unit at Flinders Medical Centre. Inclusion criteria: adult (>18 years), diagnosed with HNC and treated with curative intent, >6 months post-treatment with no evidence of residual HNC, and presenting with moderate-severe dysphagia (DIGEST Summary Grade >1). Exclusion criteria: inability to provide informed consent, history of oropharyngeal dysphagia preceding cancer diagnosis, history of neurological disorders known to cause oropharyngeal dysfunction (e.g. Parkinson's disease, cerebrovascular accident), upper oesophageal sphincter or oesophageal pathology causing dysphagia (e.g. stricture), medication known to affect swallowing function, intercurrent illness increasing procedural risk (American Society of Anaesthesiologists physical classification > III) (765), and known allergy to hyaluronic acid.

Screening for potentially suitable participants involved reviewing Flinders Medical Centre Head and Neck Cancer Clinic records between January 2019-June 2020, with 145 patients reporting dysphagia symptoms (Figure 9.1). Of these, 21 (14%) potentially suitable patients were identified, however 11 patients declined participation during the follow-up telephone call due to reasons such as increased stress levels following HNC treatment or competing priorities with work. Of the remaining ten suitable participants, three were excluded from the study due to P-HRM-I baseline study revealing pharyngeal contractile pressures within the normal range, one participant withdrew, resulting in six participants being successfully enrolled (Figure 9.1). Patient demographics, and cancer diagnosis, staging and treatment data were collected from medical record review.

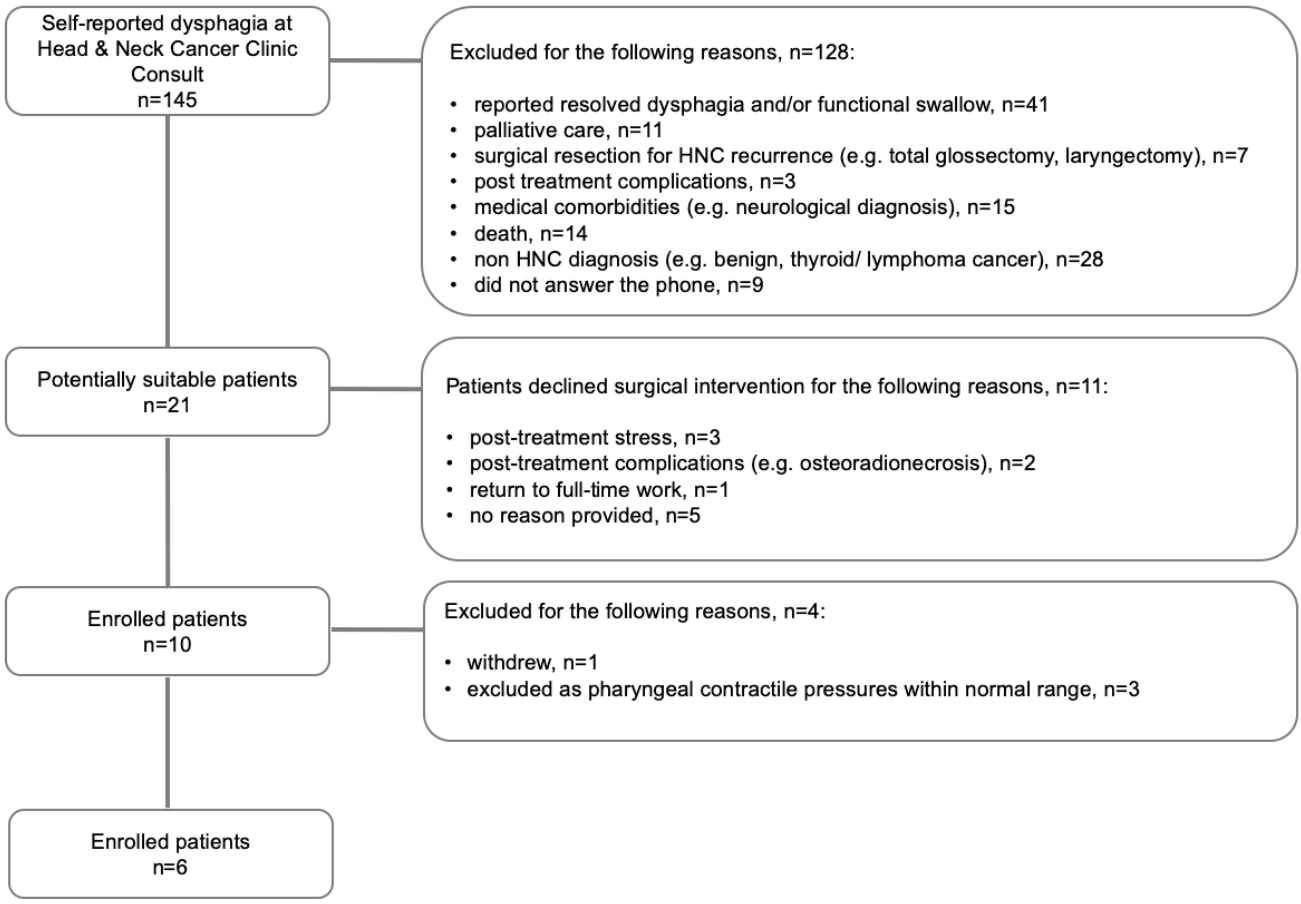

Figure 9-1PARTICIPANT SCREENING AND ENROLMENT PROCESS.

Flinders Medical Centre Head and Neck Cancer clinic records Audit between January 2019-June 2020.

Surgical Technique

Hyaluronic acid (HA), in the gel form known as Restylane® (Galderma Laboratories, USA), has been utilised in vocal fold augmentation for the treatment of glottic insufficiency (766, 767). Restylane® is considered an optimal temporary material prior to injection of a permanent filler (767) and was utilised in this study to establish the safety and feasibility of the procedure. Between 1-4 mL of Restylane® was injected into the observed tongue base deficit by a Consultant Head and Neck surgeon (Figure 9.2). A 25G needle was used with multiple passes to ensure even distribution of the tongue base. Five of the six participants had the procedure under general anaesthesia (GA), one participant had the procedure under local anaesthesia due to unsuitability for GA.

Figure 9-2 TONGUE-BASE AUGMENTATION PROCEDURE (649).

Magnetic Resonance Imaging (MRI) Measurement

Skull base Magnetic Resonance Imaging (MRI) images were collected pre-intervention and within two-four weeks following surgical intervention, and reviewed by a Radiologist. This was conducted to determine airway distance pre- and post-procedure, as well as to verify the position and volume of the hyaluronic acid post-surgery. MRI is advantageous due to good soft tissue contrast allowing for diffusion weighted imaging and multiplanar scanning (768), which is considered suitable when identifying the presence of a substance such as hyaluronic acid. The mesopharyngeal lumen distance was measured as an indirect measure of the tongue base volume in the lateral position (just left of midline).

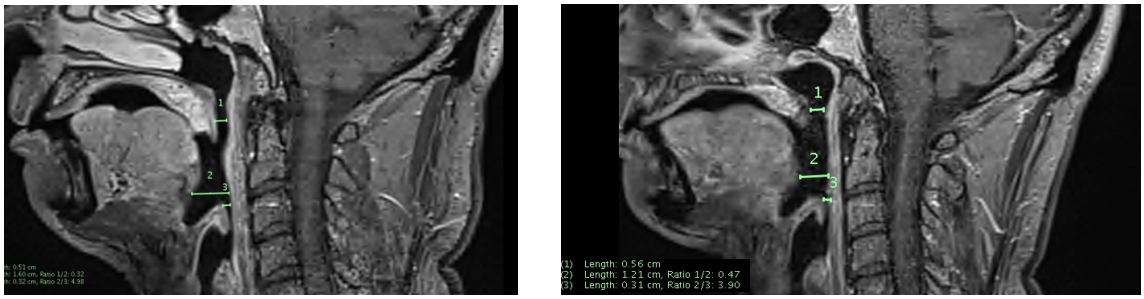

Figure 9-3 COMPARISON OF MESOPHARYNGEAL LUMEN USING MAGNETIC RESONANCE IMAGING (MRI) PRE- AND POST-TONGUE BASE AUGMENTATION PROCEDURE IN PARTICIPANT ONE.

On the pre-procedure image on the left, 2 (green horizontal line) represents the mesopharyngeal lumen measuring 16 mm; and on the post-procedure image on the right, 2 (green horizontal line) represents the mesopharyngeal lumen of 12 mm.

PROMs of Swallowing

The SSQ was used to assess self-reports of symptomatic dysphagia (651) and the FOIS (652) was used to assess clinician-rated meal status (*Section 3.4.1*).

Videomanometry Swallowing Assessments

Swallow assessments followed the standardised protocols outlined in *Section 3.4.3*. The DIGEST scale, which included the Safety, Efficiency and overall Summary Grades (482) assessed aspiration, residue and dysphagia severity, respectively (*Section 3.4.2.2*).

Analysis and statistics were conducted as described in *Section 3.5*. P-HRM-I metrics mean values were determined for 5- and 10 mL thin liquids for each participant. Median and IQR data are presented for all six participants pre- and post-procedures (Appendix 4).

9.3 Results

Six participants (all male; median age 64 years [IQR 56, 71]) completed the study. Four participants (67%) had a diagnosis of oropharyngeal cancer, two had a diagnosis of oral and nasopharyngeal cancer. Staging data were available for four participants, two (50%) were diagnosed with advanced HNC (stages III and IV). All participants had concurrent chemotherapy and radiotherapy; four of the six (67%) had tri-modality treatment with surgery in addition to chemoradiation. The median duration since HNC treatment was 47 months [IQR 8, 95 months]. All participants had tongue base augmentation with HA with a median of 2 mL [1.75, 2.5] injected. The duration for the HA procedure was approximately 10 minutes with a single night hospital admission. No adverse events were reported following the procedure.

Descriptions of the six participants are as follows and include pertinent swallow assessment findings:

Case 1

A 62 year old man who completed chemoradiation treatment for left tonsil, oropharyngeal cancer (T2N2bM0) p16+ in 2017, followed by left partial glossectomy, phrenectomy and mandibulectomy for advanced oropharyngeal cancer (T4aN1M1) in 2017 with resultant moderate dysphagia requiring tube-fed nutritional support. A 2 mL volume of HA was administered during the tongue base procedure. Mesopharyngeal lumen distance decreased on MRI (Table 9.1). P-HRM-I analysis biomechanics consisted of reduced bolus presence time, an increased UOS opening, as well as a reduction in the number of multiple swallows following the procedure.

Case 2

A 65 year old male who had concurrent chemoradiation and left tongue base resection for oropharyngeal cancer in 2007 and initially reported functional swallowing. He reported a decline in swallowing following mandibulectomy for treatment of osteoradionecrosis in 2017. He presented with the most severe dysphagia categorised as life-threatening. Despite this, he reported managing a total oral diet with the use of texture modification and compensatory strategies. A 1 mL volume of HA was injected on the left side, after which he reported improved swallowing symptoms without an increase in oral intake texture diet following the procedure. Biomechanical outcomes showed that whilst he presented with reduced pharyngeal and

mesopharyngeal pressures, all bolus propulsion measures of bolus presence time, and UOS opening extent and relaxation were improved. MSB was unchanged.

Case 3

A 48 year old male had an oral cavity, floor of mouth cancer (T2N0M0) that was managed with surgical resection in 2015, followed by recurrence in the right tongue managed with a right partial glossectomy and concurrent chemoradiation in 2016. Osteoradionecrosis was identified in 2018 and treated with a mandibulectomy and jaw replacement. Severe dysphagia requiring tube-feeding was reported following the mandibulectomy. A 2 mL volume of HA was injected on the left side. Although he reported some improvement in his swallowing following the procedure, this was not reflected in the SSQ. HPRM measures of bolus presence time, SRI and UOS relaxation pressure were improved. Number of MSB were unchanged.

Case 4

A 58 year old male who was diagnosed with an advanced left palatine tonsil, oropharyngeal cancer (T4N2M0), p16+ treated with left oropharyngectomy, parotidectomy and chemoradiation in 2018. He had a moderate dysphagia and required tube-fed nutrition. A 2 mL volume of HA bilaterally resulted in a self-reported improvement in dysphagia symptoms. Aspiration rating was increased following the HA procedure. Although mesopharyngeal and total pharyngeal pressures decreased, HPRM measures of bolus presence time, UOS opening extent and UOS relaxation pressure were improved alongside a reduction in the number of multiple swallows.

Case 5

A 71 year old male who was diagnosed with nasopharyngeal cancer (unknown staging) treated with chemoradiation in 2002. In 2014, he developed osteoradionecrosis requiring right segmental mandibulectomy with resultant moderate dysphagia requiring tube-feeding. Following a 4 mL HA procedure he reported no changes in his swallowing, despite a marginal increase in dysphagia symptoms on the SSQ. The biomechanical measures of mesopharyngeal pressures and bolus propulsion were all marginally altered.

Case 6

A 71 year old male with early-stage tonsil, oropharyngeal cancer (T2N0M0) treated with right tonsil excision and selective bilateral neck dissection and concurrent chemoradiation in 2012

with resultant moderate dysphagia. He managed an oral diet with texture modifications and compensatory strategies. Following a 2 mL volume of HA to the right tongue base he reported improved swallowing symptoms and oral intake status, with less requirements to modify the texture of his solid food. There was a marginal increase in mesopharyngeal pressure following the HA procedure, reduced bolus presence time and increased UOS opening for at least one tested volume was shown.

MRI Measurements

The pre- and post-procedure mesopharyngeal lumen measures are presented in Table 9.1. A reduction of the mesopharyngeal lumen distance following the procedure occurred in five participants. This reduction infers an increase in tongue base volume. A reduction of mesopharyngeal lumen distance of more than 2mm occurred in three of the five participants.

Table 9-1 MESOPHARYNGEAL MRI MEASUREMENTS PRE- AND POST-PROCEDURE

Participants	MRI-derived mesopharyngeal lumen measure (mm)	
	Pre-Procedure	**Post-Procedure**
1	16	**12**
2	7	7
3	6	**5**
4	22	**21**
5	9	**6**
6	7	**5**

Bold values indicate a Mesopharyngeal lumen reduction following HA injection compared with pre-procedure baseline. MRI: Magnetic Resonance imaging; mm: millimetre; HA: Hyaluronic Acid

PROMs of Oral Intake and Swallowing

The patient-reported symptomatic dysphagia scores, assessed using the SSQ, trended downwards following the HA procedure compared with baseline (Figure 9.3). Four participants reported a reduction in symptomatic dysphagia, one participant reported no change (Participant 3), and one participant reported an increase in symptoms (Participant 5). Overall, the median SSQ score pre-procedure was 1126 [925, 1279], decreasing to 820 [403, 1117] post-HA procedure but was not statistically significant (Wilcoxon Rank Test, p=0.173, t = 4). A strong correlation was observed with the total SSQ score and DIGEST Efficiency (r = 0.845, p = 0.034, Spearman's rho).

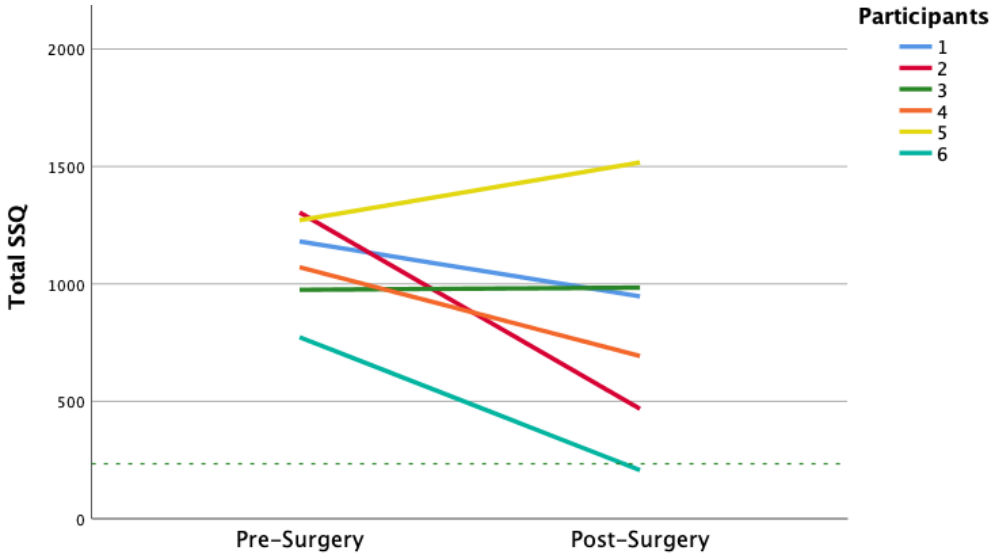

Figure 9-4 LINE-GRAPH COMPARING PATIENT-REPORTED SSQ OUTCOMES PRE- AND POST-HA PROCEDURE.

An overall reduction of dysphagia symptoms are shown. post-HA, four participants reported a reduction in dysphagia symptoms, one reported no change and one an increase in symptoms. Green dotted line represents normal threshold for dysphagia symptoms.

SSQ: Sydney Swallow Questionnaire with >234 indicative of symptomatic dysphagia (651)

Oral intake reports at baseline included four participants being tube fed dependent and two participants managing a total oral diet with some texture modifications and/or use of compensatory strategies (Table 9-2). Following tongue base augmentation, patient reported oral intake improved in two participants (Participant 1 and 6) but no change was reported in the other four participants. The overall median FOIS pre-procedure was 2 [IQR 2, 5], improving to 3 [IQR 2, 5] post-HA. A FOIS Level 3 indicates enteric tube dependency with consistent oral intake (Table 9.2).

Case	Timing	Self-Reported Oral Intake Levels	Pharyngeal Luminal Pressure				Global Function		Bolus Timing		UOS Opening Extent		UOS Relaxation		Multiple Swallows
		FOIS	Pharyngeal Contractile Integral mmHg.s.cm		Meso-pharyngeal Contractile Integral *mmHg.s.cm*		Swallow Risk Index		Bolus Presence Time *s*		UES Admittance *mS*		UES Integrated Relaxation Pressure *mmHg*		No.
			5 mL	10 mL	5 mL	10 mL	5 mL	10 mL	5 mL	10 mL	5 mL	10 mL	5 mL	10 mL	5 mL
1	Baseline	2, tube dependent/ minimal oral intake	83	98	16	30	59	13	6	4	1.9	3.7	7	3	4
	Post-HA	3, tube dependent/ consistent oral intake	80	80	6	24	19	12	2	5	2.7	4.9	11	3	2
2	Baseline	5, oral diet/ multiple consistencies + compensation	346	400	79	93	34	13	5	5	2.1	1.7	30	3	3
	Post-HA	5, oral diet/ multiple consistencies + compensation	270	223	79	73	4	2	1	1	2.7	4.1	20	10	3
3	Baseline	2, tube dependent/ minimal oral intake	140	160	33	35	47	27	3	5	3.8	3.5	11	4	1
	Post-HA	2, tube dependent/ minimal oral intake	152	138	38	28	6	9	2	0.6	3.5	3.6	5	13	1
4	Baseline	2, tube dependent/ minimal oral intake	44	41	1	4	56	109	6	6	4.1	3.4	-2	-3	2
	Post-HA	2, tube dependent/ minimal oral intake	28	31	2	0.1	10	74	0.4	1	4.1	3.1	-5	-4	1
5	Baseline	2, tube dependent/ minimal oral intake	40	53	17	19	62	175	1	3	3.9	4.8	5	5	1
	Post-HA	2, tube dependent/ minimal oral intake	60	55	21	17	54	186	2	4	3.6	3.7	2	3	1
6	Baseline	5, oral diet/ multiple	22	16	1	0	18	17	7	8	4.4	3.8	-2	-2	2

		consistencies + compensation													
	Post-HA	6, total oral diet /multiple consistencies without compensation	23	18	1	0	13	51	2	5	3.9	4.9	-2	-2	2

FOIS: Functional Oral Intake Scale; UOS: Upper Oesophageal Sphincter; HA: Hyaluronic Acid.

Light green denotes improvement and orange denotes deterioration, white denotes no change.

Swallow Assessments

Pre-procedure, simultaneous videomanometry was conducted in three of the six participants, while the other three participants had separate VFSS and P-HRM-I within 1-2 months of each other. Post-HA, five of the six participants had simultaneous videomanometry within 2-4 weeks; one participant had separate VFSS and P-HRM-I investigations within 2 weeks. During the VFSS, the standard protocol was not followed for all participants due to the severity of the participants' known dysphagia. Whilst all participants completed 5 mL and 10 mL volumes of thin liquids, three participants were unable to swallow the extremely thick liquids (IDDSI 4) and consequently swallowed mildly thick fluids (IDDSI 2) instead for all assessments. Therefore, the P-HRM-I derived data analysis presented is of 5 mL and 10 mL thin liquids only. Data from the mildly and/or extremely thick liquid swallows were amalgamated for quantification of aspiration and residue on VFSS using the DIGEST.

P-HRM-I Metrics

For the cohort, there was no significant improvement in the pharyngeal contractile integral (*Appendix 4*). There was a significant reduction in SRI in the 5 mL volume (*Appendix 4*, Figure 9.4B), but no significant findings for other P-HRM-I Core and Additional Metrics pre- and post-HA procedure.

The P-HRM-I metrics pre- and post-HA for each participant are presented in Table 9.2 with remaining P-HRM-I Core metrics presented in Appendix 5. The mesopharyngeal contractile pressures were decreased with at least one of the bolus volumes in five of the six participants following HA injection (Table 9.2; Figure 9.4a). The velo- and hypo-pharyngeal pressures were unchanged for all participants (*Appendix 5*). All six participants demonstrated a reduction of the SRI with at least one of the bolus volumes following the procedure (Figure 9.4c). This change was significant with a 5 mL volume of thin fluids ($p = 0.08$, $t=29$, Wilcoxon Rank Test), however this was not shown with a 10 mL volume (*Appendix 4*). BPT was reduced with at least one of the bolus volumes in five of the six participants following the procedure (Table 9.2; Figure 9.4b). Five participants showed an increase in the UOS opening extent with at least one of the bolus volumes (UES Max Adm; Table 9.2; Figure 9.4d), and five also showed a reduction of UOS relaxation (UES IRP) with at least one of the bolus volumes following the HA procedure (Table 9.2).

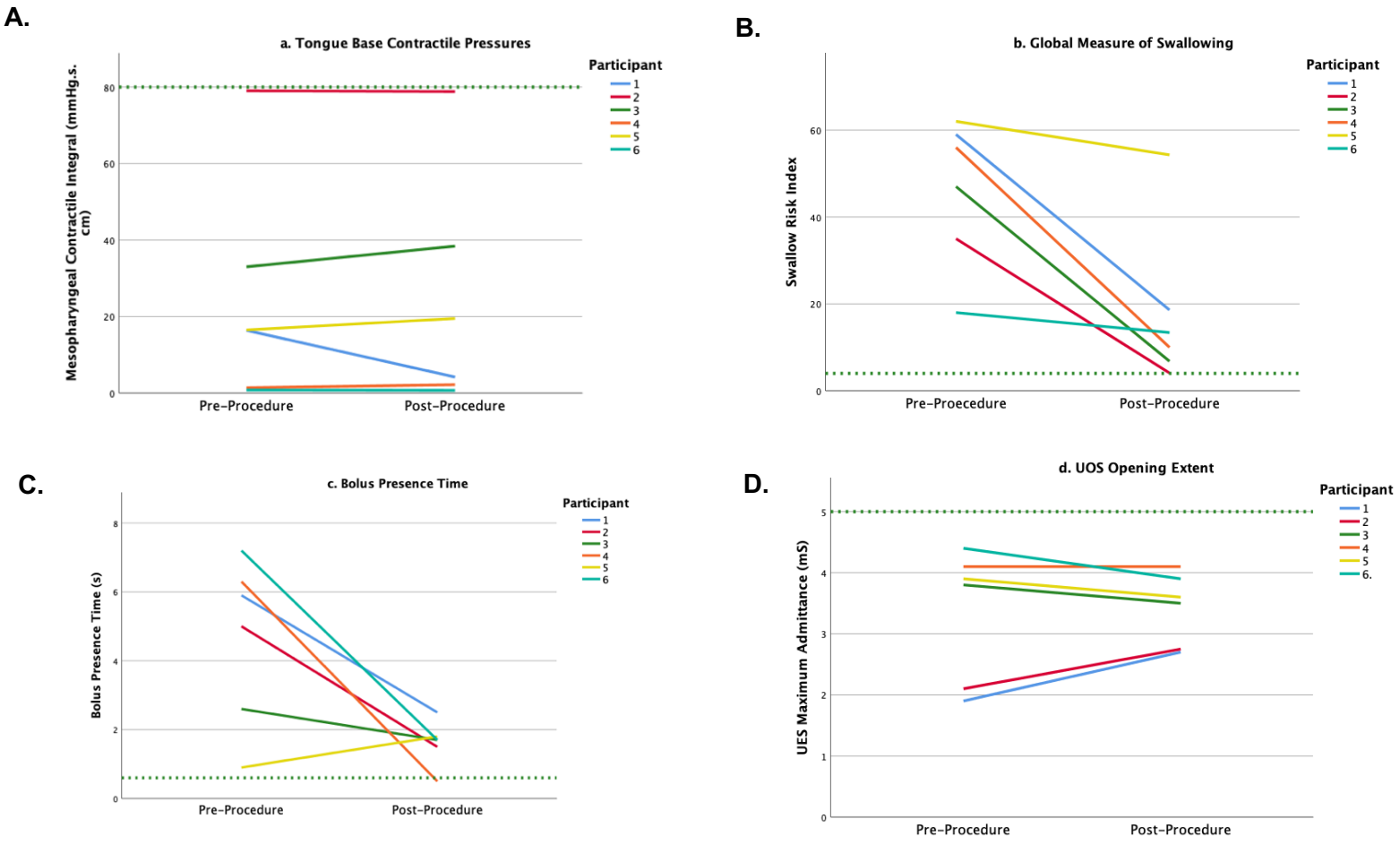

Figure 9-5 LINE GRAPHS SHOWING INDIVIDUAL PARTICIPANT RESULTS WITH 5 ML THIN LIQUIDS AT BASELINE AND POST-HA ACROSS FOUR P-HRM-I OUTCOME MEASURES.

A: Mesopharyngeal Contractile Pressures (Tongue Base contractile Pressures); B: Swallow Risk Index (global measure of swallowing function); C: Bolus Presence Time; D: UOS Opening Extent. The green dotted line indicates the mean of the normal range (544).

UOS: Upper Oesophageal Sphincter

Four participants demonstrated multiple swallowing behaviour with 5 mL volume of thin liquids at baseline, with two of these showing a reduction following the HA procedure (Table 9.2, Figure 9.5).

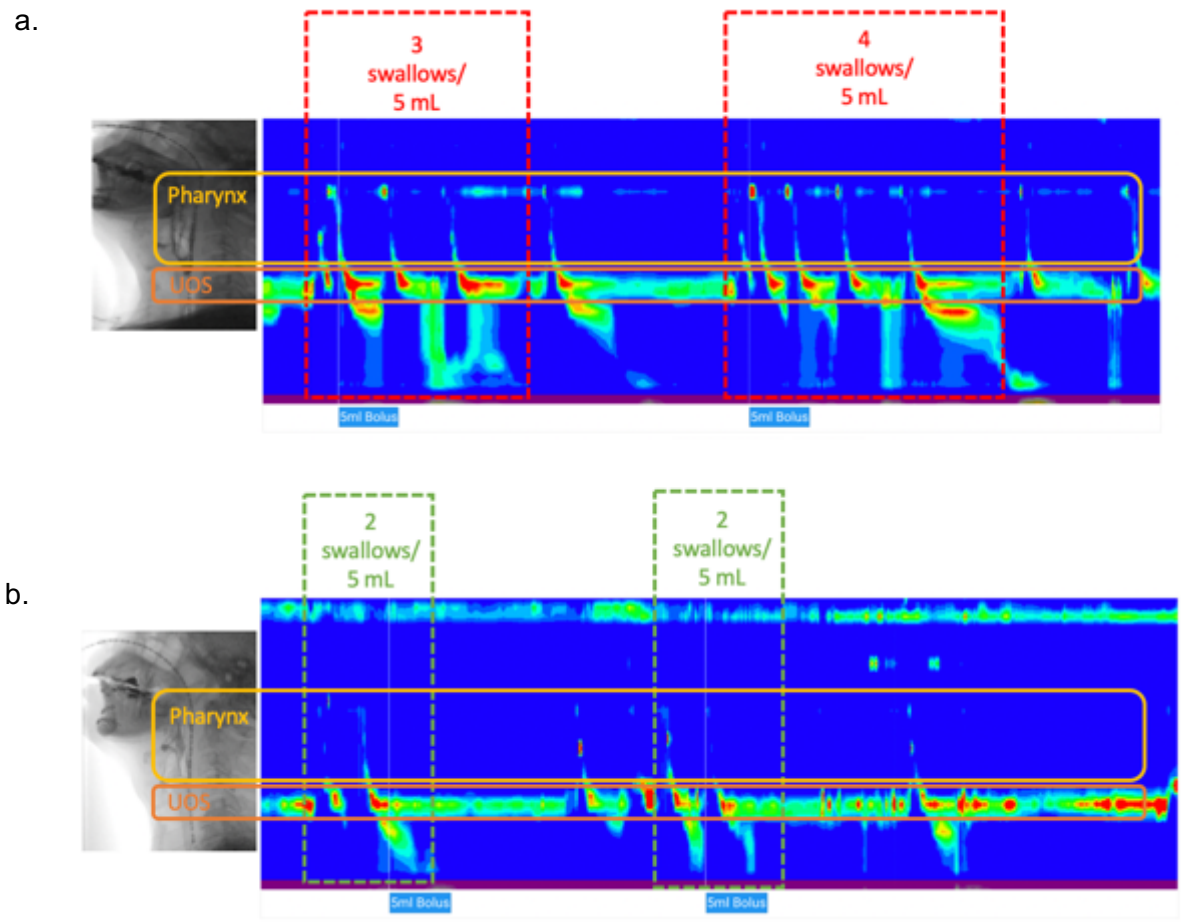

Figure 9-6 COMPARISON OF MULTIPLE SWALLOWING OF A 5 ML THIN LIQUID BOLUS AT BASELINE AND FOLLOWING THE HA PROCEDURE FOR PARTICIPANT 1.

A: Baseline VFSS image showing P-HRM-I catheter spanning the pharynx with some residue observed following 2 x swallows of a 5 mL bolus. Note on the P-HRM-I study 3-4 swallows are shown for a 5 mL bolus. B: Post-HA procedure VFSS image showing the P-HRM-I catheter spanning the pharynx with minimal pharyngeal residue following 2 x swallows of a 5 mL bolus volume. Note the P-HRM-I study identifies only two multiple swallows for a 5 mL bolus volume.

VFSS: Videofluoroscopy Swallowing study; P-HRM-I: Pharyngeal High-Resolution Manometry with Impedance

VFSS Outcomes

All six participants had moderate-life-threatening dysphagia severity at baseline (DIGEST Summary Grade; Table 9.3), with five of the six participants presenting with more than 50% pharyngeal residue (Efficiency Grade) and five of the six participants presenting with silent penetration and/or aspiration (Safety Grade). Post-procedure the pharyngeal residue rating (Efficiency Grade) was

unchanged compared with baseline in all six participants. The ratings of aspiration (Safety Grade) and overall dysphagia severity (Summary Grade) were largely unchanged post-HA procedures. The aspiration rating changed for two participants post-HA, with an increase of aspiration grade for one participant and a decrease in the other.

Table 9-3 VFSS OUTCOMES OF ASPIRATION, RESIDUE AND DYSPHAGIA SEVERITY

Case	Timing	Videofluoroscopy Swallowing Study Outcomes		
		Aspiration *DIGEST Safety Grade*	**Residue** *DIGEST Efficiency Grade*	**Severity** *DIGEST Summary Grade*
1	Baseline	2	1	Moderate
	Post-HA	2	1	Moderate
2	Baseline	3	4	Life-threatening
	Post-HA	2	4	Life-threatening
3	Baseline	2	3	Severe
	Post-HA	2	3	Severe
4	Baseline	0	3	Moderate
	Post-HA	3	3	Severe
5	Baseline	1	3	Moderate
	Post-HA	1	3	Moderate
6	Baseline	1	3	Moderate
	Post-HA	1	3	Moderate

Dynamic Imaging Grade of Swallowing Toxicity (DIGEST) (482) derived from VFSS assessment at baseline and post-HA. DIGEST scales include: Aspiration (DIGEST Safety Grade): 0=flash transient penetration above the vocal folds, 1=intermittent silent penetration to the vocal folds, 2=intermittent silent aspiration, 3= chronic silent aspiration; Residue (DIGEST Efficiency Grade): 1=10-49% residue of any bolus type, 3=50-90% residue of liquid or pudding, 4= near complete residue; and Severity (DIGEST Summary Grade). Light green denotes improvement and orange denotes deterioration, white denotes no change.

9.4 Discussion

This is the first study to investigate the biomechanical impact on the swallowing mechanism of novel tongue base augmentation for the management of moderate-severe dysphagia following HNC treatment. Swallowing assessments also incorporated self-reported measures and visual instrumental assessment, which revealed varied efficacy outcomes following the procedure. While self-reported dysphagia symptoms and P-HRM-I measures of SRI, BPT, UOS opening and relaxation improved following the procedure, MCI did not increase, and minimal observable changes were noted from VFSS-derived measures of aspiration, residue and dysphagia severity.

In an Australian context, the safety and feasibility of tongue base augmentation procedures with the temporary HA filler was demonstrated in this small cohort. Of the post-HNC treatment patients who reported dysphagia symptoms at the time of clinical review,14% were potentially suitable for tongue base augmentation treatment, which offers a therapeutic option for such patients with chronic dysphagia and few other options. The pertinent patient-reported outcome measures that were utilised before and after the HA included the SSQ and FOIS, with four of the six participants reporting a reduction of dysphagia symptoms following the procedure and two reporting an improved oral intake scale rating. Importantly, these results indicate a benefit of tongue base augmentation on symptom severity and participant experience following the procedure.

There was a significant reduction of the global measure of swallowing, the SRI, following the HA procedure when compared with baseline. Other notable P-HRM-I results included: (1) reduction of BPT; (2) increased UOS opening extent; (3) reduction of UOS relaxation; and (4) reduction of the number of multiple swallows with a 5 mL bolus volume. Collectively, these results suggest improved bolus propulsion through the pharyngeal lumen, indicating that this procedure may improve bolus transit. Multiple swallowing behaviour (MSB) is a known observation of dysphagia (734) and demonstrated in the post HNC treatment cohort (*Chapter 8*). MSB indicates difficulty with achieving complete bolus transfer with a single swallow. Four participants displayed MSB at baseline, with two demonstrating improvement following the tongue base augmentation procedure. Notably, these same two participants also reported improvements in swallowing symptoms using the SSQ following the procedure. While further research is required to confirm these findings, the potential effect of improved bolus propulsion through the pharyngeal lumen highlights the advantage of P-HRM-I assessment in detecting subtle biomechanical patterns that provide insight into the effect of treatment regimens on the swallowing mechanism.

The VFSS-derived functional bolus measures of residue and aspiration were unchanged following tongue base augmentation. The absence of change in functional outcomes may be attributed to (1)

reduced baseline pharyngeal and mesopharyngeal contractile pressures of this participant cohort compared with normative ranges, and/or (2) the small filler volume utilised in the tongue base augmentation procedure. The overall pharyngeal contractile pressure and the sub-components comprising of the velo-, meso- and hypo-pharyngeal contractile pressures were largely unchanged or modestly reduced following the procedure. This is inconsistent with our hypothesis that tongue base augmentation would result in increased pharyngeal, and in particular mesopharyngeal, pressure generation. Efficient pharyngeal bolus clearance requires adequate tongue force to generate a driving pressure behind the bolus, as well as the pressure gradient difference between the elevated tongue base pressures and the reduced pressures in the hypopharynx (103). In this cohort, five of the six participants demonstrated mesopharyngeal and total pharyngeal contractile pressures that were considerably below the normative ranges prior to the procedure (544), suggesting an inability to generate lumen occlusive pressures. The fact that these pressures did not increase following the procedure suggests that the filler volume was insufficient to overcome this marked anatomical deficit.

In this study, a median volume of 2 mL HA was injected during the procedures. This small volume resulted in a modest reduction in mesopharyngeal lumen space on MRI, indicating some increase in tongue base volume. Although the volume of HA was comparable to the lipofilling volume reported by one study (761), it was markedly less than the amount hypothesized to result in a therapeutic effect (649). Kraaijenga and colleagues (2016) conducted three sessions with 3-month intervals between each session to account for the expected reabsorption of approximately 50 per cent of the filler, resulting in a total median lipofilling volume of 30 cm^3 (649). Thus, the conservative HA injection volumes used here may have contributed to the limited effect observed on swallowing outcomes. However, this cautious approach to filler volumes was considered necessary in order to minimise patient risk during the evaluation of a novel interventional study in the Australian health care setting where possible risks of oedema-induced airway obstruction exist (761). The findings from this small study, along with an absence of adverse events, supports the safety of this novel procedure, and subsequently larger filler volumes may be considered in future studies.

Tongue base dysfunction is merely one of the reported mechanisms contributing to dysphagia in the post-HNC treatment population, with additional mechanisms including reduced pharyngeal contraction, impaired epiglottic deflection (380, 385) and reduced UOS opening (384, 739). Therefore, future studies may consider a multi-level intervention study that targets these mechanisms. This may comprise of a combined interventional approach, including: (1) tongue base augmentation with consideration of the methods and findings from this study and previous

publications (649, 761), (2) UOS endoscopic dilatation (739, 769), and (3) therapeutic swallowing exercises (645, 770). Furthermore, evaluating tongue base augmentation in post HNC treatment patients with less severe dysphagia may demonstrate more favourable effects.

This study has the following limitations: (1) a small study cohort (n=6), however this is a comparable size to the only other published cohort study (n=5) who completed tongue base augmentation using adipose tissue (649), (2) conservative volume of HA, which was based on safety considerations, however may not have been large enough to display meaningful efficacy outcomes, and (3) no QOL assessment was conducted, despite acknowledging the impact of swallowing dysfunction on QOL (400) this was not included as part of the original protocol due to the temporary nature of the HA procedure and expected minimal impact on QOL outcomes.

9.5 Conclusion

This case series demonstrates the safety and varied efficacy of the tongue base augmentation procedure using HA for the management of moderate-severe dysphagia following HNC treatment. Overall self-reported dysphagia symptoms improved following the procedure and subtle biomechanical changes were observed on P-HRM-I that suggest improvement of bolus propulsion through the pharyngeal lumen. The conservative volume of tongue base augmentation filler appeared unable to compensate for the extent of the markedly reduced pharyngeal pressure generation at baseline, resulting in negligible change on VFSS. Further research is required to understand the full effect of tongue base augmentation on swallowing.

Chapter 9 concludes the observational studies presented in this thesis. In the following Chapter, a synthesis of the key P-HRM-I metrics that were significantly altered across the four homogenous cohort studies and in the two intervention studies will be presented. Each of the P-HRM-I metrics will be defined and discussed in relation to their contribution to the identification of abnormal swallowing features in each of the studies, through which unique biomechanical pathophysiological swallowing patterns became apparent.

10. SYNTHESIS OF FINDINGS[6]

10.1 Summary

P-HRM with or without impedance operates as part of routine clinical care in only a few centres both nationally and internationally (32, 503). Although speech pathologists have conveyed interest in the contribution of P-HRM-I in the assessment and management of dysphagia, uncertainty remains regarding clinical indicators to determine suitability of use and the patient cohorts who would most benefit (771). The studies in this thesis have evaluated cohorts that often have speech pathology involvement in swallowing assessment and management. P-HRM-I has been utilised to not only characterise swallowing in these cohorts but to demonstrate the usefulness of the quantified data to identify pathophysiological impairments that may underlie dysphagia symptoms. This may assist in decision making regarding the clinical application of P-HRM-I, and the outcomes may be used to inform more tailored and effective dysphagia management (10, 22, 504, 772). The interpretation of a P-HRM-I study requires an understanding of how each biomechanical metric is derived, how it contributes to the pharyngeal swallow and what abnormal findings indicate. In this Chapter, each of the P-HRM-I metrics are discussed in relation to their contribution to the identification of abnormal swallowing features in each of study cohorts investigated, through which unique biomechanical pathophysiological swallowing patterns/outcomes became apparent. Based on the work presented throughout this thesis, the rationale and development of a classification framework is then outlined, in order to provide assistance for clinicians during P-HRM-I interpretation.

[6] The data presented in this Chapter was accepted for an **oral presentation** at the Laryngology Symposium of Australasia Virtual Conference, 2021.

10.2 Characterisation of Dysphagia using P-HRM-I Metrics

At commencement of candidature, the reporting of P-HRM with or without impedance metrics was inconsistent. This was recognised and addressed in 2019 by an international expert P-HRM-I committee who formulated consensus generated P-HRM-I Core and Additional metrics (21). The following section will discuss each of the Core and Additional metrics, outlining the metric definition and the pathophysiological impact of an abnormal finding to provide a basis for interpretation and signify its clinical relevance (Table 10.1).

Table 10-1 P-HRM-I CORE AND ADDITIONAL METRIC FINDINGS FOR OF THE COHORT AND INTERVENTIONAL STUDIES

	Core Metrics	OSA	Post-mUPPP+/-CCT	Pre- and Post-mUPPP+CCT	Critically Ill	Post-HNC treatment	Pre- and Post-Tongue Base Augmentation
P-HRM-I Core Outcome Set Metrics							
Lumen Occlusive Pressures	**PhCI** (mmHg.cm.s)	↑	↑	-	-	• 43% (6/14) had pharyngeal weakness. Not associated with residue or aspiration.	-
	VCI (mmHg.cm.s)	↑	↑	-	#		-
	MCI (mmHg.cm.s)	-	-	↓	#		-
	HPCI (mmHg.cm.s)	↑	-	↓	#		-
Distension Pressure	**IBP** (mmHg)	↑	↑	-	-	• 29% (4/14) had UOS dysfunction. • 14% (2/14) had UOS dysfunction and pharyngeal weakness.	-
UOS Opening and Relaxation	**UES IRP** (mmHg)	↑	↑	↓	↑	↑, increased aspiration	-
	UES Max Ad (mS)	↓	-	-	↓	↓, increased aspiration	-
	UES RT (s)	↓	-	-	↓	↑, increased residue	-
P-HRM-I Additional Outcome Set Metrics							
Bolus Flow Timing	**BPT** (s)	-	↓	-	↑	↑ BPT and ↓ DCL, increased pharyngeal residue	↑*
	DCL (s)	↓	↓	-	-		↓*
	UES BP (mmHg)	↓	-	-	↓	-	-

Global Measure of Swallowing	**SRI**	↑	↑	-	↑	Median value 16	↓
Lumen Occlusive Pressures	**UES Post CI** (mmHg.cm.s)	-	-	↓	#	-	-
	Prox Es CI (mmHg.cm.s)	-	-	-	#	-	-

The P-HRM-I core metrics of UOS opening and relaxation, hypo-pharyngeal intra-bolus pressure and pharyngeal lumen occlusive pressures (21) and the additional metrics including bolus flow, pre- and post-UOS pressures, global measure of swallowing (SRI) and proximal oesophageal contractile pressures (497). NB: OSA, Post-mUPPP+/-CCT, Critically ill and Post-HNC Treatment cohorts data were compared to healthy controls data (544). ↑ Indicates significant increase, ↓ Indicates significant decrease; *Indicates observed trend: increase or decrease; #: represents that those metrics not reported in this study as analysis of this cohort occurred prior to the establishment of the standardised P-HRM-I Core and Additional Metrics (21).

P-HRM-I: Pharyngeal High-Resolution Manometry with Impedance; UOS: Upper Oesophageal Sphincter; UES: Upper Esophageal Sphincter; mUPPP+/-CCT: Modified Uvulatopharyngoplasty and/or Coblation Channelling of the Tongue; HNC: Head and Neck Cancer; OSA: Obstructive Sleep Apnoea; VCI: Velopharyngeal Contractile Integrals; MCI, Mesopharyngeal Çontractile Integrals ; HPCI, Hypopharyngeal Contractile Integrals; PhCI, Pharyngeal Contractile Integral; IBP: Intra-Bolus Pressure; UES RT: UES Relaxation Time; UES Max Adm: UES Maximum Admittance; and UES IRP: UES Integrated Relaxation Pressure; BPT: Bolus Presence Time; DCL: Distention-Contraction Latency; UES BP: UES Basal Pressure; SRI: Swallow Risk Index; UES Post CI: UES Post Contractile Integral; Prox Es CI: Proximal Esophageal Contractile Integral.

10.2.1 Core Pharyngeal Outcome Measures

10.2.1.1 Core Metrics - Pharyngeal and Velo-, Meso- and Hypo-Pharyngeal Contractile Pressures

Pharyngeal lumen occlusive pressures directly measure the pressure generated by the pharynx during swallowing from the velo- to the hypo-pharynx (21). This provides the lumen occlusive pressures of the total pharynx (PhCI) as well as individual anatomical sub-components (VCI, MCI and HCI) (21). Measurement of the sub-regions of pharyngeal pressure generation is of critical importance as it enables identification of distinct pressure mechanisms during the swallow, specifically (1) velopharyngeal closure, together with a tonic UOS, provides for configuration of an enclosed pharyngeal chamber that supports the generation of pharyngeal pressure to assist with bolus propulsion (105), and (2) the driving pressure behind the bolus at the mesopharynx, together with reduced hypopharyngeal pressures (103) and activated pharyngeal constrictors, further assist with bolus propulsion (5).

Increased total pharyngeal pressures, primarily driven by higher velopharyngeal pressures, were observed in the OSA (*Chapter 4*) and post-mUPPP+/-CCT (*Chapter 5*) cohorts. Interestingly, the velopharyngeal pressures were unchanged in the matched pre- and post-mUPPP+CCT cohort (*Chapter 6*). Collectively, these results indicate that increased velopharyngeal pressures during swallowing are associated with OSA pathophysiology and remain elevated despite mUPPP surgery. In comparison, the critically ill post-extubation or decannulation cohort did not show a significant difference in total pharyngeal pressures compared to healthy controls (*Chapter 7*). This was unexpected given one of the proposed mechanisms of dysphagia in this population is neuromuscular weakness (349), hypothesized to be caused by disuse of the oropharyngeal musculature (715).

Effective bolus clearance represents the complex inter-play between the driving pressures of the tongue base, the subsequent pharyngeal stripping wave, and the UOS relaxation and opening extent (105, 737). A previous P-HRM study found reduced pharyngeal pressures in a post-HNC treatment cohort (28), but these findings were not correlated with measures of bolus-derived assessment (via impedance or visual instrumental assessments). In *Chapter 8*, half of the post-HNC treatment cohort demonstrated pharyngeal weakness with reduced mesopharyngeal contractile pressures, however this was not associated with residue or aspiration rankings on VFSS. This finding emphasises that effective clearance is influenced by multiple factors additional to the tongue base driving pressures (107).

10.2.1.2 Clinical Relevance of Pharyngeal Pressure Core Metrics

The P-HRM-I Core pharyngeal metrics in this thesis were able to provide new insight into the pharyngeal mechanisms characterising altered swallowing function in different clinical cohorts. It should be acknowledged that none of the cohorts investigated in this thesis had a neurological aetiology, such as stroke or a neurodegenerative disorder, which are often associated with pharyngeal weakness (497).

10.2.2 Core UOS Relaxation and Opening Metrics

The biomechanical metrics of UOS relaxation pressure (UES IRP), opening (UES Max Adm), and relaxation duration (UES RT), and intra-bolus distension pressure (IBP) provide quantifiable assessment of UOS function. Evaluation of the UOS function from active closure to relaxed opening requires not only the analysis of individual biomechanical measures, but also their integration. This allows the detection of key biomechanical swallow patterns (106, 121, 591).

10.2.2.1 Core Metric - UOS Relaxation Pressure

UOS relaxation pressure (UES IRP) measures the lowest pressures throughout relaxation during swallowing (21). Higher UOS relaxation pressures are suggestive of UOS restriction during bolus flow (497), which could indicate cricopharyngeus muscle relaxation impairment (152). This metric showed clear changes in each of the cohorts when compared to healthy controls or with VFSS bolus flow observations. Higher UOS relaxation pressure was observed in the OSA cohort (*Chapter 4*), following mUPPP+/-CCT surgery (*Chapter 5*) and in the critically ill cohort following extubation or decannulation (*Chapter 7*), suggesting UOS restriction during bolus flow. In the post-HNC treatment cohort (*Chapter 8*), increased UOS relaxation pressures were significantly associated with increased aspiration on VFSS, a finding that cannot be measured using visual instrumental swallowing assessments. In the interventional studies, when comparing matched pre- and post-tongue base augmentation surgery in the post-HNC treatment cohort with moderate-severe dysphagia (*Chapter 9*), UOS relaxation pressures were increased following the procedure, with increased pyriform sinus residue observed on VFSS. This finding may represent the limited effect of the conservative tongue base augmentation volume to compensate for the markedly reduced pharyngeal pressure generation. Consequently, this provided for a less effective intra-bolus driving pressure, which was unable to overcome the UOS relaxation pressures, resulting in an increase in

residue (104, 121). In the other interventional study comparing pre- and post-mUPPP+CCT outcomes (*Chapter 6*), UOS relaxation pressures were reduced following surgery approaching the normal range (544), indicating improvement of UOS restriction during bolus propulsion.

10.2.2.2 Core Metric - UOS Opening Extent

UOS opening extent is measured during bolus transit and is a correlate of UES Max Adm, which is the inverse of intra-luminal impedance (497, 591). Distinct alterations in UES Max Ad has previously been observed in cohorts with a neurological or structural aetiology (e.g. cricopharyngeal bar) (591). The OSA cohort showed a reduction of UOS opening extent (*Chapter 4*). However, this was not observed in the mUPPP+/-CCT (*Chapter 5*) or the matched pre-and post-mUPPP+CCT (*Chapter 6*) cohorts, which may represent improvement of UOS opening extent following the surgical management for OSA. The critically ill cohort following extubation or decannulation (*Chapter 7*) presented with reduced UOS opening extent, which may be consistent with the previously reported VFSS-derived finding of reduced pharyngoesophageal segment opening (333). In the post-HNC treatment cohort (*Chapter 8*), there was a significant correlation with reduced UOS opening extent and increased aspiration on VFSS. Although reduced UOS opening has previously been observed during VFSS in patients post-HNC radiation treatment (383, 386), it did not correlate with observed aspiration post HNC treatment (366, 385). This novel finding demonstrates the advantage of P-HRM-I analysis in the assessment of UOS function (741) as well as its correlation with clinically meaningful observations.

10.2.2.3 Core Metric - UOS Relaxation Duration

UOS relaxation duration (UES RT) measures the time from relaxation to contraction (21). Prolonged UOS relaxation time has been associated with observed aspiration on VFSS (567, 773). UOS relaxation duration was within normal limits in the OSA (*Chapter 4*), post-UPPP+/-CCT (*Chapter 5*) and critically ill following extubation or decannulation (*Chapter 7*) cohorts. Additionally, UES RT was unaffected by surgical intervention in the mUPPP+CCT (*Chapter 6*) and tongue base augmentation (*Chapter 9*) cohorts. Although reduced UOS relaxation time was only present in two post-HNC treatment participants (*Chapter 8*), it was positively correlated with increased pharyngeal residue and severity of dysphagia. A reduced UOS relaxation time has previously been reported in a post-HNC treatment cohort using VFSS (740), which could reflect a peripheral impairment resulting from causes such as radiation associated injury (386).

10.2.2.4 Core Metric - Intra-Bolus Distension Pressure

Intra-bolus pressure is a single point measurement defined at the mid-point of the bolus at the hypopharynx (104, 497, 774). In the event that the UOS is narrowed, the intra-bolus pressure will increase as there is an increased resistance of bolus movement through the smaller structure (UOS) resulting in an increased intra-bolus pressure gradient (737). Increased IBP values may reflect reduced UOS opening diameter and/or reduced UOS distension (159, 497, 499), which may be attributed to altered swallow modulation or anatomical causes, such as cricopharyngeal bar or UOS fibrosis (497). Increased IBP was present in the OSA (*Chapter 4*) and post-mUPPP+/-CCT (*Chapter 5*) cohorts only. In the OSA study, a sub-group of participants had a VFSS that was simultaneously conducted with P-HRM-I, whereby anatomical abnormalities were not observed. Thus, it is inferred that increased IBP was most likely due to altered swallow modulation. Although the IBP was increased in the post-mUPPP+/-CCT cohort, in the intervention study assessing pre- and post-mUPPP+CCT outcomes (*Chapter 6*) IBP was unchanged following surgery. Collectively these results indicate that the increased IBP is a feature of OSA.

10.2.2.5 Clinical Relevance of UOS Core Metrics

The P-HRM-I Core UOS Relaxation and Opening outcome measures in this thesis provide new and important insights into the competence of UOS function across different clinical cohorts. When evaluated individually and together, these measures identify important biomechanical swallow patterns and highlight why these metrics should be measured and reported in routine analysis (21). The precise assessment of UOS function using P-HRM-I is advantageous compared with VFSS-derived measures, which are largely considered to provide subjective interpretation (741, 775). VFSS assessment only provides measures of UOS opening and duration, which requires application of specific software (480, 481). This may be a reason why UOS function is not consistently reported on by speech pathologists during VFSS assessment (776), resulting in variable interpretation and management (777).

10.2.3 Additional P-HRM-I Outcome Measures

The Additional P-HRM-I measures overall had variable contribution to the understanding of underlying swallowing abnormalities. The bolus timing measures and Swallow Risk Index provided valuable insights, however, the additional UOS and proximal oesophageal pressure measures were largely unremarkable across each of the studied cohorts.

10.2.3.1 Additional Metrics - Bolus Presence Time and Distension Contraction Latency

Bolus timing measures, recorded in milliseconds, include: (1) Bolus Presence Time (BPT), which measures the time of the bolus in the pharynx, and (2) Distension Contraction Latency (DCL), which measures the timing from pharyngeal distension to pharyngeal contraction (544). A prolonged BPT and/or shortened DCL may indicate an impaired ability for the modulation of the swallow mechanism associated with altered sensory afferent function (497, 612). Prolonged BPT may suggest early bolus arrival due to premature spillage and/or bolus residue in the pharynx following the swallow (497), and may be comparable with visual instrumental findings of increased bolus dwell time in the pharynx prior to laryngeal vestibule closure (581, 681, 778). A shortened DCL is indicative of discoordination of bolus timing in the pharyngeal contraction sequence, likely resulting from pressure generation due to pharyngeal contractile pressure rather than the driving pressure of the tongue base behind the bolus (497, 581). Alternatively, a short BPT together with a short DCL may indicate impaired modulation of the swallow motor program to sensory inputs, which could be attributed to a central rather than peripheral affect (612, 779).

BPT and DCL provided pertinent insights into the altered pharyngeal swallowing mechanism in all the studies reported in this thesis. A shortened DCL was observed in the OSA cohort when compared to controls (*Chapter 4*), which is not surprising given that previous studies identified sensory impairment associated with swallowing dysfunction in patients with OSA (272, 278). Although altered bolus flow timing measures were observed in the OSA and post-mUPPP+/-CCT cohorts (*Chapter 4 and 5*, respectively), these were not present in the matched pre- and post-mUPPP+CCT cohort (*Chapter 6*), demonstrating that mUPPP+CCT surgery does not impact the timing of bolus propulsion relative to the pharyngeal contraction sequence. Prolonged BPT was observed in the critically ill following extubation or decannulation cohort when compared to healthy controls (*Chapter 7*), which is consistent with visual instrumental swallowing outcomes of delayed laryngeal closure and swallow onset (329, 330). Interestingly, a shortened DCL was associated with prolonged endotracheal intubation duration, which may reflect the reported effects of prolonged use of sedation and neuromuscular blockers (612) necessary for intubation maintenance. The post-HNC treatment cohort (*Chapter 8*) demonstrated both a shortened DCL and an increased BPT, which were significantly associated with increased pharyngeal residue on VFSS, suggestive of a pharyngeal sensory impairment. In the matched pre- and post-tongue base augmentation cohort (*Chapter 9*), a trending reduction of BPT and an increase of DCL was noted, suggestive of an improvement of bolus flow following the procedure. This finding, along with the trending improvement in the number and type of multiple swallowing behaviour (MSB), is suggestive of an increased relative bolus volume being propelled through the pharynx during a single swallow with an associated increase in pharyngeal distension pressures.

10.2.3.2 Additional Metric – Swallow Risk Index

The SRI provides a quantitative value representative of global pharyngeal swallowing function derived from integrated pressure and impedance data. An SRI of 15 or more is indicative of dysphagia with an increased probability of aspiration (567). Although the SRI has not been reported as an indicator of severity of pharyngeal dysphagia, the findings presented in this thesis across the varying cohorts spanning the severity continuum demonstrates its potential functionality for this purpose.

The SRI discriminated subtle differences between healthy controls and cohorts with sub-clinical swallowing changes, including the OSA (*Chapter 4*) and the post-mUPPP+/-CCT (*Chapter 5*) cohorts. In the critically ill following extubation or decannulation cohort (*Chapter 7*), the two participants with an SRI of 15 or more were later confirmed to be aspirating. Interestingly, a recent case report of a critically ill patient with COVID-19 found a significant correlation with elevated SRI and aspiration on VFSS (717). In the post-HNC treatment cohort (*Chapter 8*), the median SRI value of 16 was suggestive of disordered swallowing with increased aspiration risk, which showed a positive correlation with the DIGEST Safety scale (482).

The two interventional studies illustrated the application of the SRI as a global measure of pharyngeal swallowing. In the matched pre- and post-mUPPP+CCT cohort (*Chapter 6*), the SRI did not increase following surgery indicating unchanged swallowing function, which was also reflected by no change in self-reported dysphagia symptoms following surgery. Following tongue base augmentation in the post-HNC treatment cohort with dysphagia (*Chapter 9*), improvement in the SRI indicated improvement in pharyngeal swallowing, which was mirrored in the trend of reduced self-reported dysphagia symptoms following the procedure.

Overall, the Additional P-HRM-I measures of altered bolus flow (BPT and DCL) and SRI provided pertinent findings of the abnormal swallow mechanism across the cohorts investigated. The data from this thesis highlights the utility of these Additional impedance-derived P-HRM-I metrics and support the recommendations of these measures being considered as Core measures in the future.

10.2.3.3 Additional Metrics – UOS and Proximal Oesophageal Pressure Measures

The Additional UOS and proximal oesophageal pressure metrics include: (1) UOS pre-swallow pressure (UES Basal Pressure), (2) post-UOS contractile pressures (UES post contractile integral pressure), and (3) proximal oesophageal contractile integral (Prox Es CI) (497, 544). These

measures were largely unremarkable across the cohorts investigated. UOS basal pressures are considered a non-specific feature of neurogenic swallowing dysfunction (154, 591) and a reported effect of sedation and analgesia (612). UES BP was only reduced in the OSA cohort (*Chapter 4*) and the critically ill following extubation or decannulation cohort (*Chapter 7*). In the OSA cohort, reduced UES BP could suggest neurogenic involvement, particularly given the indication of sensory impairment associated with OSA (272, 278). In the critically ill following extubation or decannulation cohort, a reduced UES BP may be representative of the effect of sedation and analgesia (612).

The UOS post-swallow pressure (UES CI) measures the UOS pressures generated during the swallow sequence following transit of the bolus through the UOS. An increase UES CI was shown in healthy controls when swallow volume increased, and is representative of the 'grabbing' effect of the UOS during laryngeal descent to prevent retrograde bolus movement to the pharynx immediately following the swallow (164, 544). Thus, a reduction of the UES CI may suggest an impairment of the UOS which could result in increased pharyngeal residue or mis-direction to the laryngeal airway (164). A change in UES post-CI was only demonstrated in the pre- and post-mUPPP+CCT cohort (*Chapter 6*) where it was reduced following surgical intervention. This observation may suggest that the mUPPP+CCT surgery is associated with altered laryngeal descent affecting the UOS contraction following the swallow. The proximal oesophageal swallowing pressures did not show any significant changes in any of the studies included in this thesis. There is a paucity of reporting of the Prox Es CI (553, 780) and the clinical relevance therefore remains unclear. This may be due, in part, to the proximal oesophagus not being considered part of standard pharyngeal swallow assessment. Additionally, proximal oesophageal contractility (as measured by the Prox Es CI) is not integrated in the standard interpretation of the classification of oesophageal motility (781). These limited findings support these P-HRM-I measures being categorised within the P-HRM-I Additional Metrics.

10.3 Proposal of a P-HRM-I Classification Framework

A recognised barrier to the clinical translation of the P-HRM-I technology into clinical practice for the assessment of dysphagia is the lack of support or guidance for the analysis and interpretation of the P-HRM-I swallow study (772). A classification framework is considered necessary to address this barrier to assist in the interpretation of P-HRM-I findings to enable clinicians to describe abnormal swallowing features in a manner that provides a uniform understanding.

In the studies presented in this thesis, novel and distinct biomechanical patterns were observed in different clinical cohorts across the dysphagia severity continuum. These patterns are characteristic of swallowing alterations within each cohort and are discussed below. These are important findings that contributed to the formation of the classification framework.

10.3.1 Biomechanical Patterns Identifying UOS Restrictive Disorders

UOS dysfunction is a component of pharyngeal dysphagia. However, UOS function is not routinely assessed by speech pathologists during VFSS assessment (776, 777), with reasons outlined in *Section 10.2.2.5*. The studies presented in this thesis showed indicators of UOS restriction in each of the cohorts investigated, providing a marker of overall pharyngeal function that is not often described. It is therefore valuable to discuss these findings in more detail in the setting of a proposed classification framework.

The P-HRM-I criteria for neurogenic UOS dysfunction were recently described (624). This included the requirement of abnormal values of two or more of the four UOS Core metrics, specifically increased UES IRP, reduced UES Max Ad, abnormal (short or prolonged) UES RT and increased IBP (624). Accordingly, in the OSA (*Chapter 4*), post-mUPPP+/-CCT (*Chapter 5*) and the critically ill following extubation or decannulation (*Chapter 7*) cohorts, two or more abnormal UOS measures were present. This UOS dysfunction most likely represents a neuroregulatory impairment of the UOS (104, 106). This type of impairment may cause the central nervous system to produce a swallowing motor response that less efficiently accommodates the bolus volume and consistency. In contrast, the pre- and post-mUPPP+CCT cohort demonstrated a reduction of UOS relaxation pressures approaching normal limits and no additional altered UOS metrics (*Chapter 6*), suggesting that while a degree of UOS restriction during bolus flow is present, it does not interfere with the neuroregulatory mechanisms of the cricopharyngeus muscle (579).

Approximately half of the post-HNC treatment cohort had two or more abnormal UOS metrics indicating UOS dysfunction (*Chapter 8*), which is consistent with previously reported VFSS findings

(382, 738, 773). This likely represents the effects of chronic radiation on the pharyngoesophageal segment with increased fibrotic tissue, loss of vascularity, and loss of muscular and peripheral neurological attenuation (370). Evaluating the correlation of VFSS bolus flow and P-HRM-I measures, increased aspiration was significantly associated with UOS dysfunction, an observation supported by others (719, 773). UOS dysfunction was characterised by a reduction of UOS opening extent and an increase of UOS relaxation pressure during swallowing. Although the exact mechanism is unclear, this finding demonstrates the impairment of bolus direction towards the UOS with misdirection to the laryngeal inlet resulting in aspiration (164).

10.3.1.1 Considerations of Abnormal UOS Metrics Interpreted with Abnormal Pharyngeal Metrics

Alterations in UOS metrics require interpretation together with pharyngeal metrics to differentiate the mechanistic breakdown. For example, reduced UES maximum admittance (591) and elevated IBP (561) individually could indicate a primary UOS impairment but could also indicate a pharyngeal impairment that impacts UOS function. This is seen when pharyngeal pressures are insufficient to achieve efficacious bolus propulsion, resulting in UOS bolus flow restriction. Also, reduced UOS opening diameter may suggest either reduced pharyngeal contractility pressure and/or be representative of UOS bolus flow restriction (591). However, when two or more UOS metrics signify UOS dysfunction, the mechanistic breakdown is more likely to be at the UOS.

The OSA (*Chapter 4*), post-mUPPP+/-CCT (*Chapter 5*) and critically ill following extubation or decannulation (*Chapter* 7) cohorts demonstrated pharyngeal contractility pressures within or above the normal range. Therefore, reduced UOS opening diameter in these cohorts is considered a definitive representation of UOS bolus flow restriction. Similarly, approximately half of the post-HNC treatment cohort (*Chapter 8*) demonstrated UOS dysfunction without pharyngeal weakness; only two participants presented with simultaneous pharyngeal weakness and UOS dysfunction. Thus, whilst this may represent a true UOS bolus restriction with simultaneous pharyngeal weakness, cautious interpretation is recommended. In particular, increased IBP as a metric recognised to contribute to UOS dysfunction has shown reduced validity in the presence of reduced pharyngeal pressures (561).

10.3.2 Biomechanical Patterns Identifying Abnormal Pharyngeal Contractile Pressures

Reduced pharyngeal constriction implies pharyngeal weakness that is predictive of aspiration on VFSS (782, 783) and has been commonly observed in VFSS assessments in heterogenous cohorts with dysphagia (582, 784). Whilst pharyngeal constriction measures on VFSS have been validated using low-resolution manometry (122) and correlated with the pharyngeal squeeze manoeuvre during FEES assessment (785), it has not been validated using P-HRM-I. Utilisation of P-HRM-I omits the need for inferring pharyngeal strength with visual instrumental assessment and allows for direct measurement of the pharyngeal contraction and relaxation across time, including at the velum, mesopharynx and hypopharynx (21). These direct measurements of pressure and relaxation allowed for the identification of the novel findings of increased total pharyngeal pressures in the OSA (*Chapter 4*) and post-mUPPP+/-CCT (*Chapter 5*) cohorts. Importantly, it also demonstrated adequate pharyngeal pressures in the critically ill following extubation or decannulation cohort (*Chapter 7*). In the post-HNC treatment cohort (*Chapter 8*) pharyngeal weakness was identified, however this did not correlate with residue or aspiration rankings on VFSS. This highlights that effective bolus clearance is influenced by multiple factors in addition to pharyngeal contractile pressures (107).

10.3.3 P-HRM-I Classification Framework

The identified biomechanical swallowing patterns described above contribute to the proposal of a P-HRM-I Classification Framework for the interpretation of pharyngeal swallowing. This Framework only comprises of the recommended P-HRM-I Core Metrics (21) that have been advocated for standardised reporting. Whilst some Additional Metrics demonstrated clinical relevance across the cohort studies, these would not be internationally reported and have therefore not been incorporated into the Framework.

This proposed P-HRM-I Classification Framework (Figure 10.1) aims to recognise the two broad categories of biomechanical abnormality revealed from the cohort studies: (1) Pharyngeal Propulsive Disorders, characterized by evidence of impaired pharyngeal contractility, and (2) UOS Restrictive Disorder (786), a type of UOS dysfunction. This Framework aims to provide terminology describing the biomechanical pathophysiological impairment that can be applied consistently for clinical interpretation of P-HRM-I studies.

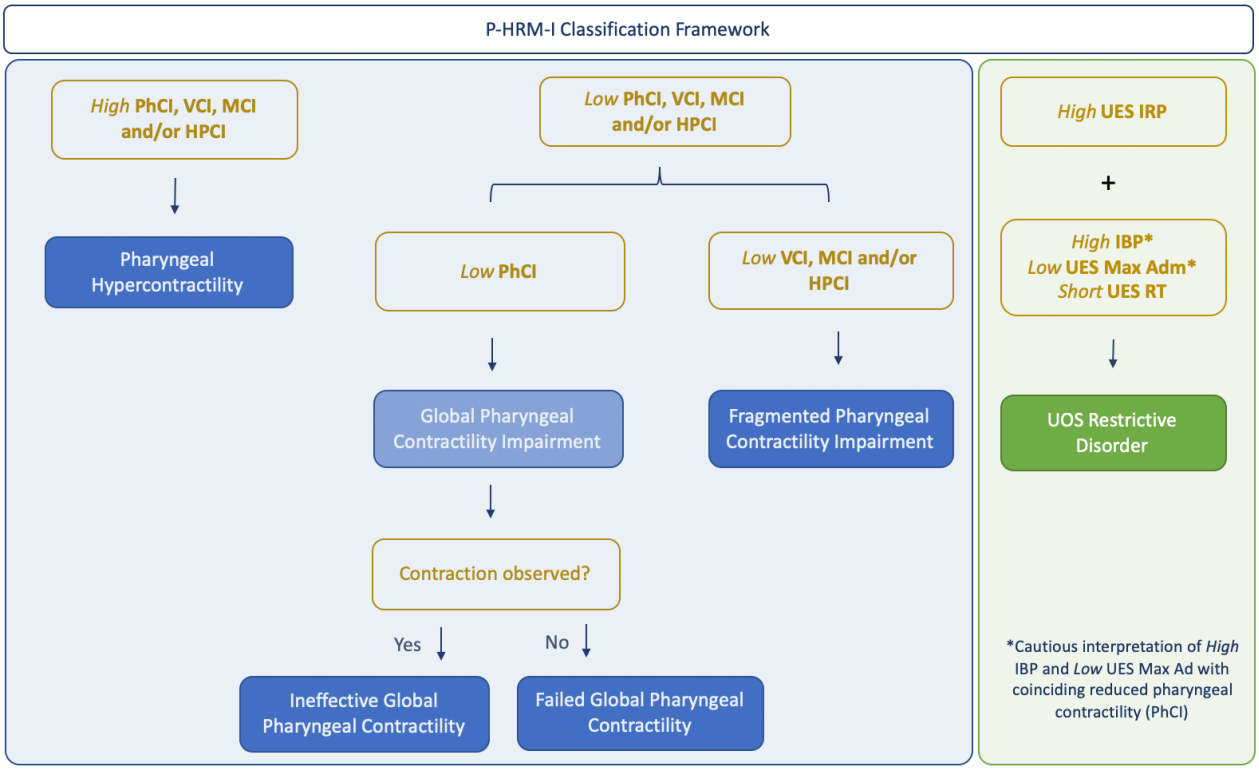

Figure 10-1: PROPOSED P-HRM-I CLASSIFICATION FRAMEWORK.

Blue box represents pharyngeal metrics with pharyngeal propulsion impairment framework; and the green box represents UOS metrics to assist in UOS restrictive disorder assessment.

PhCI: Pharyngeal Contractile Integral; VCI: Velopharyngeal Contractile Integral; MCI: Mesopharyngeal Contractile Integral; HPCI: Hypopharyngeal Contractile Integral; UOS: Upper Oesophageal Sphincter; UES: Upper Oesophageal Sphincter, IBP: Intra-Bolus Pressure, Max Adm: Maximum Admittance, RT: Relaxation Time.

10.3.4 Pharyngeal Propulsive Disorders

In this framework, a pharyngeal propulsive disorder is characterised by abnormal pressure generation of the pharyngeal contractile sequence from the velo-pharynx through to the hypo-pharynx. This can be determined globally (PhCI) or in relation to anatomical sub-components (VCI, MCI and HCI) and assessed as absent, abnormally low, or normal. A global pharyngeal contractility impairment consists of reduced contractility in a sub-component (VCI, MCI and/or HPCI) and reduced total pharyngeal contractility (PhCI). A global pharyngeal contractility impairment may be classified as either: (1) *Failed* global pharyngeal contractility, which indicates failure of lumen occlusion throughout the total pharyngeal chamber, or (2) *Ineffective* global pharyngeal contractility, which indicates low lumen occlusive pressures throughout the pharynx that are otherwise appropriately sequenced. An anatomical velo-, meso- and/or-hypo-pharyngeal contractility (VCI, MCI and/or HPCI) impairment without reduced total pharyngeal contractility (PhCI) is classified as:

Fragmented pharyngeal contractility impairment, which indicates absent or low pressures in particular anatomical regions where lumen occlusive pressures are globally normal.

Pharyngeal hypercontractility of the total pharynx or the anatomical sub-components of the velo-, meso- and/or hypo-pharynx may demonstrate elevated pressures above the normative values. This is classified as pharyngeal *hypercontractility*, indicative of excessive lumen occlusion through the total pharyngeal chamber and/or in the anatomical regions.

10.3.5 UOS Restrictive Disorders

In this framework, a UOS restrictive disorder is defined as a type of UOS dysfunction that can be used as a marker of pharyngeal swallowing. A UOS restrictive disorder is characterised by an increased UES IRP with an additional abnormal UOS Metric. UES integrated relaxation pressure (UES IRP) suggests UOS restriction based on an increased value above normal and was consistently elevated across the four homogenous cohorts studied (Table 10.1). A further abnormal UOS P-HRM-I Core metric is necessary for an assessment of an UOS Restrictive Disorder, including: *short* UES relaxation time, *high* intrabolus distension pressure (IBP) and/or *low* UES maximum admittance (UES Max.Adm) (624). Although a UOS restrictive disorder is defined as a type of UOS dysfunction, this Framework does not represent severe UOS dysfunction caused by pathologies such as UOS stricture. This is a recognised limitation of the Classification Framework in its current form and future studies should incorporate further elements to the Framework to address this.

An important note of caution has been included on the Framework for the interpretation of UOS restriction when high IBP (561) and low UES Max Ad (591) occur with associated inadequacy of pharyngeal propulsion. The predictive value of IBP for detecting restricted UOS opening diminishes when bolus propulsion by pharyngeal contractile pressures is inadequate. However, in the context of pharyngeal contractility that has failed, is ineffective or is fragmented, an UOS restrictive outcome may also occur.

10.3.6 Application of P-HRM-I Classification Framework to Thesis Cohorts

The P-HRM-I data presented in this thesis demonstrated novel and distinct biomechanical patterns across different cohorts. In the non-interventional studies, these were characterised as: (1) altered UOS function with increased velopharyngeal contractile pressures in the OSA and post-mUPPP+/-

CCT cohorts, (2) altered UOS function and increased bolus presence time in the critically ill cohort following extubation or decannulation, and (3) reduced pharyngeal contractile pressures with or without UOS dysfunction in the post-HNC treatment cohort. The P-HRM-I Core metric data from the cohorts investigated were entered into the proposed P-HRM-I Classification Framework to describe the resulting biomechanical pathophysiological impairment (Figure 10.2). It is evident that each cohort presented with a UOS Restrictive Disorder, albeit with different biomechanical indicators. The cohorts in this thesis have the following classification according to the Framework:

1. OSA cohort (Figure 10.2a): Pharyngeal hypercontractility with a UOS restrictive disorder.
2. Post-mUPPP+/-CCT cohort (Figure 10.2b): Pharyngeal hypercontractility with a UOS restrictive disorder.
3. Critically ill following extubation or decannulation cohort (Figure 10.2c): UOS restrictive disorder.
4. Post-HNC treatment cohort (Figure 10.2d): Variable pharyngeal propulsive disorders with or without a UOS restrictive disorder.

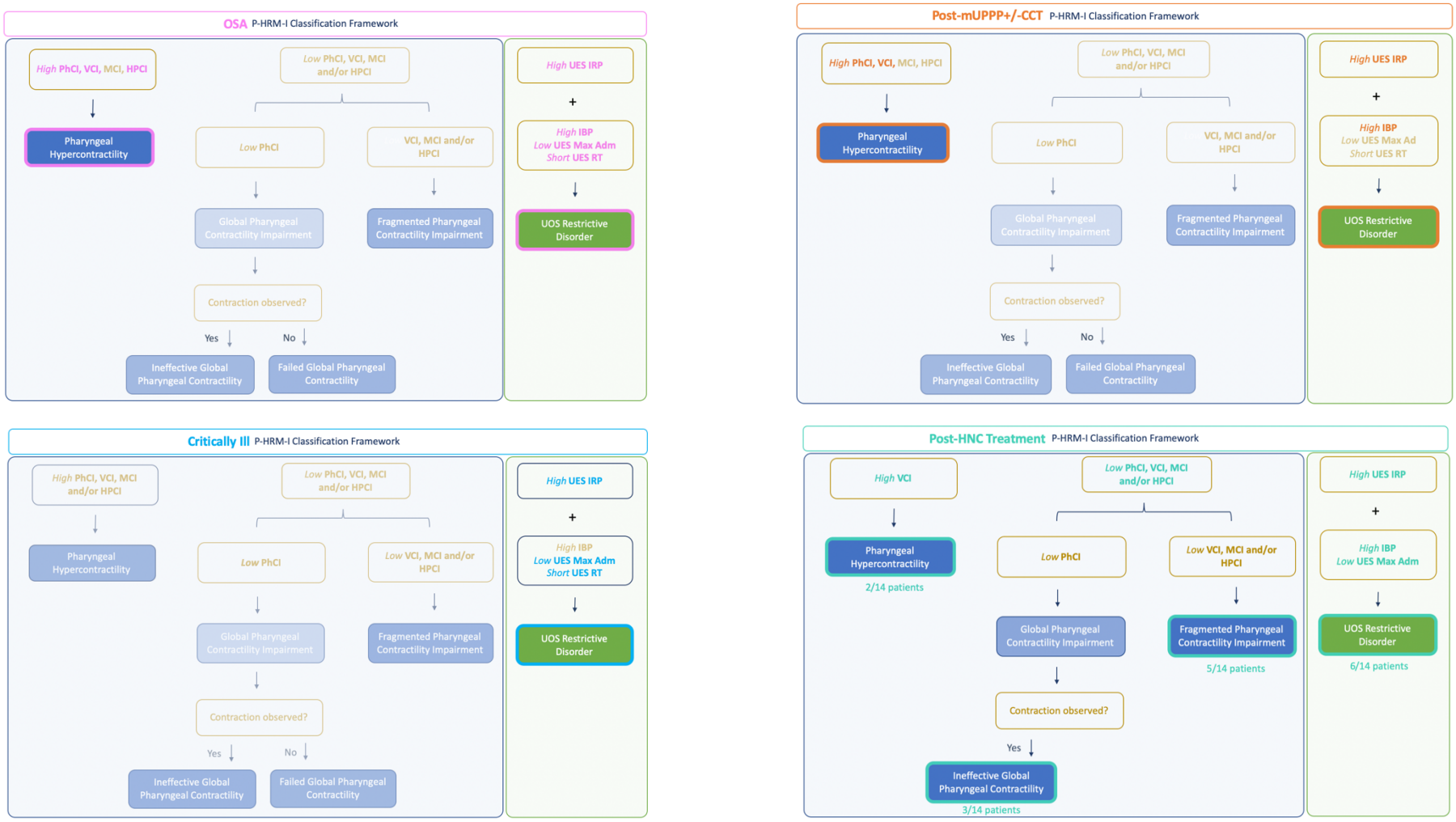

Figure 10-2 P-HRM-I CLASSIFICATION FRAMEWORK DISPLAYING THE DIFFERENT PARTICIPANT COHORTS.

A: OSA; B: post-mUPPP+/-CCT; C: critically ill following extubation or decannulation; D: post-HNC treatment cohorts.

OSA: Obstructive Sleep Apnoea; mUPPP+/-CCT: Modified Uvulatopharyngoplasty and Coblation channelling of the tongue; HNC: Head and Neck Cancer

This conceptual framework presents unified terms describing biomechanical pathophysiological impairments leading to pharyngeal dysphagia. Validation of such a Framework is required. Future studies could also identify thresholds for the individual metrics and include other participant cohorts, such as dysphagia associated with a neurological aetiology (e.g. stroke).

In Chapter 10, each of the P-HRM-I metrics were discussed in relation to their contribution to the identification of abnormal swallowing features in each of the four observational study cohorts and the two interventional study cohorts, followed by the rationale for, and proposal of, a P-HRM-I Classification Framework to assist with interpretation of P-HRM-I swallow assessments. In the following Chapter, each of the thesis studies will be discussed, with an interpretation of the salient findings relative to available literature. This includes an evaluation of the utility of P-HRM-I in the assessment of pharyngeal dysphagia, which is crucial given the potential of this technology to enhance the evaluation of swallowing.

11 DISCUSSION

11.1 Overview

Dysphagia is a symptom resulting from impairment or disorder affecting the structure or function of the preparatory oral, oral, pharyngeal and/or oesophageal phases of swallowing. Currently, dysphagia is assessed using non-instrumental clinical swallowing assessment (397) and visual instrumental swallowing assessments of FEES and VFSS, however the limitations of each of these techniques are recognised (394) (*Section 1.4.5*). VFSS is considered the gold-standard of swallowing assessment, with penetration, aspiration and residue considered the most relevant outcomes. However, VFSS has no universally accepted set of quantitative measures (10), which results in variability in interpretation and subsequent treatment planning (394, 471). In contrast, P-HRM-I provides precise, objective and quantative measures of pharyngeal and UOS pressure that is integrated with bolus transit (21, 497, 500) that can enhance the evaluation of swallowing (22, 495).

11.2 Cohort Studies

There have been 33 studies evaluating pharyngeal dysphagia associated with differing aetiologies using P-HRM-I technology, of which only 15 (45%) have used concurrent impedance acquisition (1, 26, 30, 154, 558, 561, 563, 567, 572, 581, 583, 591, 600, 603, 606)(*Appendix 1).* The overall aim of this thesis was to address this knowledge 'gap' by determining the P-HRM-I measures and patterns that may distinguish and characterise dysphagia in homogeneous adult cohort of differing medical aetiologies. The following discussion provides evidence of addressing this overarching aim. P-HRM-I-derived measures reported in this thesis provide new mechanistic insights into the altered pharyngeal swallowing in the four cohorts. This considerable body of work expands the current understanding of altered swallowing in these groups, which to date has been formed from patient-reported outcome measures of swallowing and visual instrumental swallowing assessments.

11.2.1 OSA

In the OSA population, alterations in swallowing associated with OSA are becoming more widely recognised, however the mechanisms that contribute to altered swallowing have not been established (247, 276). In *Chapter 4*, the P-HRM metrics from participants with moderate-severe OSA were compared to healthy controls, resulting in identification of biomechanical swallowing patterns contributing to dysphagia. These patterns were characterised by reduced UOS opening diameter and UOS restriction during bolus flow, with an associated elevation of bolus distension pressure at the hypopharynx and increased velopharyngeal contractile pressures. This is categorised as pharyngeal hypercontractility with a UOS restrictive disorder in accordance with the Classification Framework (*Section 10.3*). These findings could represent a neuroregulatory impairment of UOS function, which would support current hypotheses that neural injury associated with OSA causes sensory impairment and peripheral disturbances in swallowing (272, 274, 277-279). The patterns observed using P-HRM-I highlights a swallowing motor response that less efficiently accommodates for bolus volume and consistency in participants with OSA. These novel biomechanical results advance the understanding of the mechanisms that characterise altered swallowing in patients with OSA, which is a step towards addressing a knowledge gap in this population (787). Further, these findings demonstrate the potential for P-HRM-I measures to identify subclinical changes in swallowing (597).

11.2.2 Post-OSA Surgery

Dysphagia has historically been reported following OSA surgery (248, 636), however these reports commonly used VFSS assessment following historical surgical techniques including complete uvula and excessive velar tissue resection (294, 295, 313, 636). Consequently, it was unknown whether previous publications accurately represented swallowing following contemporary surgical procedures for OSA, such as mUPPP+/-CCT. In *Chapter 5*, swallowing biomechanics were assessed post-mUPPP+/-CCT surgery and compared to healthy controls. Pertinent biomechanical outcomes revealed velopharyngeal contractile pressures that remained elevated post surgery compared to controls, which is categorised as pharyngeal hypercontractility with a UOS restrictive disorder in accordance with the Classification Framework (*Section 10.3*). This is an important finding as it differs to previous reports of velopharyngeal insufficiency following historical surgical techniques of the palate for OSA (312). When considered together with the higher velopharyngeal contractile pressures identified in the OSA cohort compared to healthy controls in *Chapter 4*, these results suggest of biomechanical patterns associated with pre-existing OSA, rather than resulting from the mUPPP+/-CCT surgery. This data provides new insight, which differs from historical reports, of dysphagia evaluated following surgical management for OSA and therefore highlights the need for continued evaluation of swallowing outcomes following changes to surgical techniques.

11.2.3 Critically Ill

In the critically ill population following extubation or decannulation, aspiration is the most frequently reported primary outcome measure (346). However, the mechanisms that result in aspiration or altered swallowing at the time of extubation or decannulation are seldom studied or discussed (349). In Chapter 7, distinct biomechanical patterns were identified that characterise dysphagia in this cohort. These included increased BPT and altered UOS function, defined by reduced UES Max Adm and shortened UES RT, which is categorised as a UOS restrictive disorder in accordance with the Classification Framework (*Section 10.3*). These P-HRM-I findings support previously reported visual instrumental assessment observations in this cohort. For example, the increased BPT result is comparable with the noted VFSS outcome of increased bolus time in the hypopharynx prior to swallow initiation (329, 330) and may reflect the effects of sedation, analgesia and partial neuromuscular blockers (90, 612, 613). Similarly, the reduced UOS opening (UES Max Adm) measure with P-HRM-I is consistent with the previously reported VFSS finding of shortened pharyngoesophageal segment opening (333). However, an unexpected biomechanical finding in this cohort was the total pharyngeal pressures, which did not show a significant reduction following

extubation or decannulation. This finding challenges one of the proposed mechanisms of dysphagia in this population, whereby disuse of the oropharyngeal musculature (715) has been hypothesised to cause neuromuscular weakness (349). This novel finding highlights the utility of P-HRM-I to quantify swallowing outcomes and reveal biomechanical insight into the mechanisms that contribute to dysphagia.

11.2.4 Post-HNC Treatment

The mechanisms contributing to dysphagia have frequently been reported in the post-HNC treatment cohort, likely due to the well documented impact of dysphagia on quality-of-life in this population (378, 639, 640). Key contributing mechanisms, predominantly described from VFSS assessment, include tongue base dysfunction, reduced pharyngeal contraction, reduced epiglottic movement and reduced UOS opening (366, 380-388). In *Chapter 8*, P-HRM-I analysis of a post-HNC treatment cohort that presented with moderately severe pharyngeal dysphagia with a high prevalence of aspiration demonstrated variable pharyngeal propulsive disorders with or without a UOS restrictive disorder. Of the two distinct altered biomechanical patterns identified: (1) UOS restrictive disorder and (2) reduced pharyngeal contractile pressures; only UOS restrictive disorder was correlated with observed pharyngeal residue and aspiration on VFSS. This correlation highlights the contribution of UOS function, including the degree of UOS relaxation and opening, to effective bolus flow through the pharyngeal chamber (105, 737). To our knowledge, this is the first study to demonstrate an association between pharyngeal residue and UOS restrictive disorder in a homogenous post-HNC treatment cohort, although it has previously been reported in heterogenous cohorts (585, 742). Reduced pharyngeal contractile pressures were also identified using P-HRM-I, however these did not correlate with pharyngeal residue. This finding differs to previous studies that reported an association of pharyngeal residue with reduced pharyngeal propulsion and contractile vigour interpreted from VFSS in post-HNC treatment cohorts (382, 383, 385). However, these studies did not use P-HRM-I analysis and the contrasting findings likely reflect the inherent limitations of VFSS to assess pharyngeal pressures and analyse UOS function (741, 775), underscoring the utility and importance of P-HRM-I in this setting. These findings extend upon the results of a recent P-HRM-I study that also found reduced pharyngeal pressures in a post-HNC treatment cohort (28) by examining the relationship of the pharyngeal and UOS pressure and impedance derived metrics with VFSS derived measures of aspiration and residue to comprehensively characterise dysphagia in this cohort.

11.3 Intervention Studies

The evaluation of biomechanical measures before and after an intervention serves the purpose of demonstrating the true effect of the intervention on swallowing (587). Without comparison to baseline measures, the intervention effects can only be indirectly inferred based on other functional changes, e.g. bolus flow or occurrence of penetration/aspiration. P-HRM-I provides a precise quantification of swallowing biomechanics and is an ideal assessment technique to detect alterations in swallowing physiology following an intervention, including subtle and sub-clinical changes (27, 624, 626, 628, 629, 631, 632). It can also enhance the evaluation of swallowing by VFSS and FEES assessments (22, 495). Therefore, the secondary overall aim of this research program was to explore the utility of P-HRM-I as an interventional outcome measure and identify the biomechanical changes following an intervention to evaluate the mechanistic effect on swallowing. The use of P-HRM-I with and without impedance as an interventional outcome measure in cohort studies has been reported in seven studies. Interestingly, six have been published since 2019 (624-627, 629, 630), likely representing the increased recognition of this technology to evaluate the effectiveness of an intervention (21). In this thesis, P-HRM-I swallowing metrics were used to inform evaluation of two surgical interventions on swallowing outcomes that have not previously been reported, including: (1) pre- and post-surgical management for OSA (*Chapter 6*), and (2) pre- and post-tongue base augmentation procedure for dysphagia following HNC treatment (*Chapter 9*).

11.3.1 Pre- and Post-mUPPP+CCT Surgery

The prospective evaluation of swallowing pre- and post-upper airway surgical intervention for the management of OSA has been conducted in two previous studies (290, 314). However, these studies used VFSS and did not report on outcomes following the mUPPP+CCT surgical technique. Although both studies evaluated swallowing outcomes across different surgical techniques, no significant VFSS-derived swallowing changes were reported following OSA surgery (290, 314). In *Chapter 6*, P-HRM-I results pre- and post-mUPPP+CCT surgery in a moderate-severe OSA cohort identified key biomechanical outcomes following surgery, including: (1) velopharyngeal contractile pressures were unchanged, (2) meso- and hypo-pharyngeal contractile pressures were reduced, and (3) UOS relaxation pressures were reduced. The velopharyngeal findings suggest that the mUPPP surgery did not impair pressure generation at the velopharynx. This is a noteworthy finding because it contrasts with a previously reported notion that velopharyngeal soft tissue volume reduction (288) due to the surgery may result in reduced pressure generation. However, it has been recently reported that the velopharyngeal soft tissue volume reduction is minimal (788), which

suggests that the mUPPP may instead increase the velum tension. The reduced meso- and hypo-pharyngeal contractile pressures suggest that the CCT technique may reduce force generating capacity of these regions. However, it is important to note that whilst these pressures were reduced following surgery, they remained within normal limits (544). The reduction in UOS relaxation pressures following surgery, which approached the normative ranges (544), may indicate a degree of UOS restriction without UOS dysfunction. This finding could be representative of two mechanisms: (1) potential recovery of UOS function, or (2) an indirect result of reduced bolus propulsion due to reduced mesopharyngeal pressure generation. The biomechanical findings outlined above provide a quantified evaluation of the effect of mUPPP+CCT surgery on swallowing that has not previously been detected by other swallowing assessment techniques.

11.3.2 Pre- and Post-Tongue Base Augmentation

Tongue base augmentation is a novel procedure for dysphagia management following HNC treatment that aims to target reduced mesopharyngeal contractile pressures due to tongue base dysfunction that contribute to dysphagia (380, 647). Although two small case series have reported positive functional swallowing outcomes following tongue base augmentation (648, 649), evaluation of the swallowing biomechanics have not been studied using P-HRM-I. In *Chapter 9*, P-HRM-I swallow assessments were conducted which suggested some improvement in the outcome measures of UOS opening and relaxation following the tongue base augmentation procedure compared to baseline. These findings may suggest a subtle improvement of a more efficient transit of the bolus through the UOS. Along with biomechanical analysis, VFSS-derived outcomes were also assessed which showed no change in aspiration and residue following the procedure compared to baseline. This VFSS finding differs to previous reports whereby reduced penetration and/or aspiration was observed following tongue base injection (649), but this is likely attributable to the conservative injection volumes in our study, which likely limited the effect of tongue base augmentation on functional swallowing outcomes.

11.4 Future Directions

Throughout this program of research, the advantages and utility of P-HRM-I to enhance the interpretation of other swallowing assessment techniques is demonstrated with the use of quantified pressure and bolus flow outcomes. P-HRM-I offers potential benefits for translation into the clinical setting, through the provision a comprehensive swallowing assessment that can identify alterations in swallowing biomechanics to inform tailored management. P-HRM-I is currently considered an emergent area of practice for speech pathologists for pharyngeal swallowing assessment and is not yet widely used in routine clinical practice (22, 24). This may be in part because of the lack of a classification scheme that could support the clinical interpretation of P-HRM with or without impedance metrics and pressure topography plots. In contrast, the internationally recognised classification scheme (Chicago Classification) has facilitated the application of the HRM-I technology in the assessment of *oesophageal* motility, which is now considered the gold-standard of oesophageal assessment (781). It is likely that a comparable system for interpretation of pharyngeal motility would similarly facilitate more widespread uptake of this technology into clinical practice. Indeed, there appears to be interest by speech pathologists in using P-HRM-I as a tool for swallowing assessment (495). Therefore, based on the unique clinical data generated in the course of this research program, a P-HRM-I Classification Framework is proposed to assist clinicans with the interpretation of P-HRM-I swallow assessment studies.

11.4.1 P-HRM-I Classification Framework

Quantitative measures derived from P-HRM-I assessment may provide the most comprehensive insight into pharyngeal physiology and pathophysiology (22). The P-HRM-I Core Metrics, derived from international expert consensus, provide a standardised approach for reporting biomechanical swallowing data (21) and allows for synthesis of findings within and across cohorts. Going forward, exploring methods to increase the application of this technology to the clinical setting are warranted. A P-HRM-I Classification Framework, such as the one proposed in this thesis, is one method of bridging the gap between a research tool and clinical application. Formalising a universally accepted Classification Framework, ideally by an international expert working group, would enable clinicians to easily interpret P-HRM-I findings and identify the key biomechanical breakdown in the swallow mechanism on an individual patient level, and facilitate tailored treatment or intervention. Simplifying the clinical interpretation of P-HRM-I findings is key to increasing uptake of this technology in the clinical setting. Further validation and refinement of the proposed Classification Framework is necessary prior to its release for clinical use and this should be the focus of future research. Evaluation of additional cohorts, such as participants with neurological

and/or neurodegenerative disorders, should also be considered in future research with these findings and could be included in the Classification Framework.

11.4.2 Videomanometry

Visual instrumental assessment is considered the gold-standard of swallowing assessment. While recognizing abnormal bolus flow findings using these methods is important, they do not necessarily identify, or quantify, the underlying pathophysiological mechanisms leading to these abnormalities. P-HRM-I can provide this biomechanical understanding of the pathophysiological breakdown in the swallowing mechanism. Therefore, correlation of P-HRM-I biomechanical data with simultaneous visual instrumental swallowing assessment is recommended, to provide enhanced understanding when interpreting visual instrumental findings (495). A combined videomanometry swallowing assessment was first proposed with the use of conventional manometry technology (502) and more recently with P-HRM-I (31). This combined modality of assessment identifies both the dysphagia presentation and underlying contributory biomechanics. In order to maximise the effectiveness of videomanometry outcomes, the development of a standardised method of reporting the results should be considered. This could include correlation of P-HRM-I Core and/or Additional metrics with (1) VFSS derived bolus flow outcomes of penetration, aspiration and residue using the PAS (455) or the DIGEST (482), and/or (2) correlation with the nominal assigned scales of defined pharyngeal dysfunction using MBSImp tool or the quantified measures of timing and displacement (60, 480). The derivation of clinically meaningful VFSS measures, validated using low-resolution manometry, was published as a surrogate measure of pharyngeal strength (122). Moving forward, repeat studies incorporating these protocols with P-HRM-I would increase understanding of biomechanical outcomes in the clinical setting, which may further improve clinician reliability measures (503). Interestingly, no published studies have evaluated simultaneous P-HRM-I with FEES outcomes. This may be due to the known limitations of FEES being unable to provide a lateral view of the oropharyngeal and UOS structures (441). However, the advantages of FEES, like P-HRM-I, being an ambulatory swallow assessment means that it does not require the additional and expensive resources of VFSS assessment (10, 441) allowing future research to target this knowledge gap.

11.4.3 Modification of P-HRM-I Additional Metrics to Improve Clinical Applicability

In *Chapters 10.2.4 and 10.2.5*, the P-HRM-I Additional Metrics of Swallow Risk Index (SRI) and bolus timing measures (BPT, DCL) were proposed to be considered for future inclusion as Core

Metrics for standardised reporting. Furthermore, the development of the SRI as a clinically meaningful marker of dysphagia severity should be evaluated in future research. This may include defining SRI thresholds for the severity of dysphagia, including sub-clinical, mild, moderate and severe classifications, which may be measured against existing validated severity scales specific to homogenous cohorts such as HNC (482) and stroke (789). The severity of pharyngeal dysphagia is a critical outcome measure that signifies the degree of effect of different influences on swallowing. Currently, the severity of dysphagia is often determined clinically according to the level of food and fluid modifications required (652) and the ranking of aspiration and residue observed on visual instrumental swallowing assessments (482). Once validated against these standard clinical criteria, the biomechanically derived SRI also has the potential to represent the severity of dysphagia.

The impedance-derived bolus timing measures of BPT and DCL showed altered findings across each of the four cohort studies and the two interventional studies presented within this thesis. These metrics provided important insights into the biomechanical dysfunctions in these cohorts. Inclusion of these metrics into the P-HRM-I Core Metrics could potentially add value in understanding mechanistic abnormalities across other dysphagia cohorts. Future studies could also consider modifying or developing bolus timing metrics to determine more clinically relevant information. For example, the ability to quantify bolus dwell time (192) would involve calculating the BPT from the time the bolus is present in the hypopharynx to the onset of UOS relaxation. An additional metric that could also add value could provide the time from UOS relaxation to pharyngeal contraction. These become clinically relevant measures that are representative of the adequacy of swallow initiation.

11.4.4 P-HRM-I to Inform Individualised Therapy

Findings from P-HRM-I assessment are highly clinically relevant, because identifying precise biomechanical alterations can inform patient-centred dysphagia management (628, 631). In the post-HNC treatment cohort (*Chapter 8*), whilst VFSS-derived abnormal bolus flow observations of aspiration and residue were frequent, biomechanical data showed that approximately half of the participants presented with pharyngeal propulsive impairment and half presented with UOS restrictive disorders. Identification of the underlying impairment can lead to tailored rehabilitative swallow exercise therapy. Individual differences were also seen in the pre- and post-mUPPP+CCT cohort (*Chapter 6*). Whilst this cohort overall demonstrated a significant drop in the UES IRP following surgery, two participants showed an increase in UES IRP following surgery, which identifies two individuals who would benefit from a different therapy to the rest of the cohort. Currently, there are few studies evaluating swallowing exercises with P-HRM-I, and these have

been conducted in healthy participants (614, 618). Going forward, P-HRM-I should also be considered as an outcome measure for swallowing exercises for people with dysphagia. This would provide increased understanding of the effects of rehabilitative therapy on swallowing and hence further develop the evidence base for existing interventions, which is critically lacking (790).

11.4.5 Establishing P-HRM-I Service for Dysphagia Assessment

P-HRM-I is considered an emergent scope of practice for speech pathologists in the USA (24). However, as a speech pathology service it is integrated in few centres internationally (772). In Australia, although Speech Pathology Australia (SPA) recognises P-HRM-I as an additional swallowing assessment, there is little detail or guidance regarding its application or standards (25). This reflects the minimal availability of P-HRM-I services currently in Australia, with only one known centre in St Georges Hospital, Sydney, New South Wales where a speech pathologist contributes to the P-HRM-I assessment and interpretation. The clinical value of P-HRM-I is acknowledged by SPA and there is potential for uptake of P-HRM-I in other centres nationally, however, further infrastructure, training and competency processes and standards are required.

A P-HRM-I credentialing process at an organisational level with a defined scope of practice guideline in agreement with Gastroenterology and/or ENT medical units supporting the speech pathology profession in this emergent technology would address one of the barriers to broader adoption of this technology. Currently in Australia, P-HRM-I is conducted by trained nursing staff or technicians placing the P-HRM-I catheter and acquiring the study, with the analysis being completed by the gastroenterologist and/or speech pathologist. The P-HRM-I procedure requires insertion of an 8 or 10Fr catheter through the oropharynx and below the UOS. This may be likened to the insertion of a 14Fr nasoendoscope when conducting a FEES assessment, which is a procedure that trained speech pathologists can perform. Speech pathologists are required to complete an annual FEES credentialing process at an organisational level for authority of practice (791). A similar credentialing process for P-HRM-I would ensure standards are set and maintained. Accessibility and maintenance of P-HRM-I equipment together with a criteria guiding the suitability of P-HRM-I swallowing assessment should be implemented within an existing dysphagia assessment service (772). Speech pathologists with specialist interest in dysphagia and who have been trained in both VFSS and FEES are likely the most suitable professionals to conduct and interpret P-HRM-I (32) in the context of dysphagia assessment and management in the clinical setting.

The analysis of P-HRM-I data can be complex and may be a barrier that limits the broader adoption of P-HRM-I in the clinical setting. The cloud-based online analysis platform swallowgateway.com™(792) has the potential to be harnessed for the speech pathology professional to develop P-HRM-I analysis and interpretation skills. The ability to upload de-identified patient studies that can be shared with experts in P-HRM-I analysis has the potential to support and develop speech pathologists' knowledge and understanding of P-HRM-I analysis and identify any gaps in knowledge while ensuring accuracy of result interpretation. Additionally, the platform provides the ability to share patient studies and their results across disciplines, as well as an ability to upload other swallowing assessments that may have been conducted, such as visual instrumental assessments and PROMs. This can further support an inter-disciplinary approach to swallowing assessment and management.

11.4.6 Healthcare System

Dysphagia is a recognised chronic health condition that is associated with increased health care expenditure (8, 238, 793). The Australian healthcare system is reportedly under increased pressure and in the future, inter-disciplinary service delivery measurement models will need to address key issues of resource allocation and demonstrate patient outcomes (794). Thus, it is foreseeable that Australian policymakers will require patient specific outcomes to justify the funding allocation for management of chronic conditions (795, 796) such as dysphagia. Although it has not yet been evaluated, optimising dysphagia assessment could lead to more tailored and effective patient management, which is attractive not only for individual patients but the healthcare system more broadly. A multi-disciplinary service delivery model for swallowing assessment and management (402, 786, 797, 798) includes the provision of specialist services in the Australian healthcare system (799). The integration of P-HRM-I assessment within an existing dysphagia multi-disciplinary service can provide a quantified method to demonstrate abnormal swallowing biomechanics that, when combined with PROMs and bolus measures such as aspiration and residue (via FEES or VFSS), will likely provide the best possible swallowing assessment service. Additionally, the robust swallowing outcomes produced from such a specialist service could further support a rationale for allocation of funding for assessment and management services within specific patient cohorts and/or for specific interventions. Moving forward, consideration of the use of cloud-based platforms, such as swallowgateway.com, could be explored for the collection of big data sets that could be useful for healthcare outcome evaluation (10).

11.5 Limitations

The methodological limitations specific to each of the studies are detailed in the respective chapters. It is prudent, however, to acknowledge the pertinent limitations within and across the studies presented in this thesis. The limitations in the homogenous cohort studies include:

(1) visual instrumental assessment was conducted in a subset of OSA participants (*Chapter 4*) but was not conducted in the post-mUPPP+/-CCT (*Chapter 5*) or the critically ill following extubation or decannulation (*Chapter 7*) studies. This precludes the ability to correlate any observed visual findings with P-HRM-I metrics. Given the common use of VFSS and FEES in clinical practice, the inclusion of concurrent visual instrumental swallowing assessment with P-HRM-I would likely assist in further clinical interpretation of the P-HRM-I findings (495);

(2) the mismatched BMI of healthy controls and the OSA and post-mUPPP+/-CCT cohorts (*Chapters 4 and 5*, respectively) is a noteworthy limitation given that obesity has been associated with changes in pharyngeal swallowing (674);

(3) in the critically ill following extubation or decannulation cohort (*Chapter 7*), the P-HRM-I metrics of sub-pharyngeal contractile integrals were not included because the analysis and publication of the findings occurred prior to publication of the P-HRM-I Core metrics by the International Working Group (21). In this same cohort, longitudinal data to establish whether changes in swallowing mechanism were temporary or permanent were not collected, and this should be considered for future studies given that self-reported symptomatic dysphagia can persist at 6 months post hospital discharge (348); and

(4) in the post-HNC treatment cohort (*Chapter 8*), participants had varying sites of HNC. Given that the oropharynx is the leading anatomical site for HNSCC in a younger cohort (743), a homogenous group undergoing chemoradiation treatment is recommended in future studies. Future studies evaluating dysphagia in homogenous cohorts should consider further exploration of the identified altered biomechanical features presented in this thesis to direct hypothesis-driven protocols in the application of repeat studies.

The limitations in the two interventional studies include:

(1) The small number of participants in both studies resulted in underpowered results (*Chapters 6 and 9*). However, the pre- and post-tongue base augmentation cohort (*Chapter 9*) was a comparable size to the only other published cohort study (649) and may be a result reflective of the novelty of the procedural approach for dysphagia management;

(2) Visual instrumental swallowing assessment was not included in the pre- and post-mUPPP+CCT (*Chapter 6*) study, which raises limitations on clinical interpretation as described above; and

(3) No QOL assessments were conducted. In the post-tongue base augmentation (*Chapter 9*) study, the impact of swallowing dysfunction on QOL was acknowledged (400) however not included as part of the original protocol due to the temporary nature of the HA procedure and the minimal expected impact on global QOL outcomes within the 2-4 week timeframe. Instead, swallow symptom scores were collected.

CONCLUSION

P-HRM-I is gaining increasing recognition as a valuable swallowing assessment method that can provide precise and quantitative measures of swallowing biomechanics. Unlike other swallowing assessment methods, P-HRM-I can identify and localise alterations in the swallowing mechanism and determine the underlying pathophysiological breakdown contributing to dysphagia, which provides considerable opportunity for clinical application. Throughout this thesis, compelling examples are provided of the utility of P-HRM-I to provide new insight and further understanding of swallowing mechanisms in homogenous clinical cohorts and as an intervention outcome assessment. The value of P-HRM-I for dysphagia assessment is demonstrated across different dysphagia severities, from sub-clinical in the OSA cohort to moderate-severe in the post-HNC treatment cohort. In the cohorts with worse dysphagia severity, P-HRM-I was able to identify the mechanistic breakdown in swallowing contributing to dysphagia. P-HRM-I was able to detect biomechanical sub-clinical changes in swallowing physiology that have not previously been described in the literature with other swallowing assessment techniques. These subtle biomechanical findings demonstrate the limitations of bolus flow outcomes of aspiration, residue and premature spillage as detected with VFSS in a cohort with a sub-clinical presentation, illustrating the superiority of P-HRM-I for providing mechanistic understanding. The precision of P-HRM-I technology was advantageous in both of the intervention studies demonstrating its accurate and quantifiable value when used as an assessment method to compare pre- and post-intervention outcomes.

The P-HRM-I metrics presented in this thesis demonstrated novel and distinct biomechanical patterns that characterized dysphagia in various homogenous cohorts. These novel findings are important for the provision of meaningful translation of P-HRM-I technology into the clinical setting. In the homogenous clinical cohort studies, these were characterised as: (1) pharyngeal hypercontractility and UOS restrictive disorder in the OSA and post-mUPPP+/-CCT cohorts, (2) UOS restrictive disorder in the critically ill cohort following extubation or decannulation, and (3) variable pharyngeal propulsive disorder with or without UOS restrictive disorder in the post-HNC treatment cohort. To lay a foundation for addressing a barrier for the clinical uptake of P-HRM-I, these novel findings informed development of the proposed P-HRM-I Classification Framework to assist in the interpretation of P-HRM-I swallow assessment studies. The Framework functions to support the identification of the biomechanical impairment of the swallowing mechanism, which can

assist clinicians in determining the most tailored and efficacious treatment plan for each individual presenting with dysphagia symptoms.

Personal Final Remarks

This research program originated from my interest in dysphagia assessment and management. I have demonstrated the utility of P-HRM-I in adult dysphagia assessment in providing precise pressure and impedance measures across various clinical cohorts revealing novel findings that have direct clinical relevance. While I acknowledge that my thesis is broad, it reflects the extent of dysphagia assessment that speech pathologists encounter, which highlights the application of P-HRM-I in different settings as well as for dysphagia assessment across broad aetiologies and severities. While the studies presented in this thesis focus on the analysis of biomechanical measures in homogenous cohorts and the utility of P-HRM-I as an interventional outcome measure, I hope to extend this research and correlate P-HRM-I findings with visual instrumental swallowing assessments and swallow rehabilitation exercises. I believe future application of this technology will provide increased depth of understanding of the mechanistic factors contributing to dysphagia and will lead to the building of an evidence base that has the potential to support increased clinical uptake of this technology and ultimately optimise the assessment and management of people presenting with dysphagia.

REFERENCES

1. Schar M, Woods C, Ooi EH, Athanasiadis T, Ferris L, Szczesniak MM, et al. Pathophysiology of swallowing following oropharyngeal surgery for obstructive sleep apnea syndrome. Neurogastroenterol Motil. 2018;30(5):e13277.

2. Shaker R, Cook I, Dodds WJ, Hogan WJ. Pressure-Flow Dynamics of the Oral Phase of Swallowing. Dysphagia. 1988;3:79-84.

3. Dodds WJ. The Physiology of Swallowing Dysphagia. 1989;3:171-8.

4. Lear CSC, Flanagan JB, Moorrees CFA. The Frequency pf Deglutition of Man. Archives of Oral Biology 1965;10:83-99.

5. Kahrilas P, J., Logemann J, A., Lin S, Ergun G, A. Pharyngeal Clearance During Swallowing: A Combined Manometric and Videofluoroscopic Study. Gastroenterology. 1992;103:128-36.

6. Eslick GD, Talley NJ. Dysphagia: epidemiology, risk factors and impact on quality of life--a population-based study. Aliment Pharmacol Ther. 2008;27(10):971-9.

7. Roden DF, Altman KW. Causes of dysphagia among different age groups: a systematic review of the literature. Otolaryngol Clin North Am. 2013;46(6):965-87.

8. Attrill S, White S, Murray J, Hammond S, Doeltgen S. Impact of oropharyngeal dysphagia on healthcare cost and length of stay in hospital: a systematic review. BMC Health Serv Res. 2018;18(1):594.

9. Cook IJ, Kahrilas PJ. AGA technical review on management of oropharyngeal dysphagia. Gastroenterology. 1999;116(2):455-78.

10. Ciucci M, Jones CA, Malandraki GA, Hutcheson KA. Dysphagia Practice in 2035: Beyond Fluorography, Thickener, and Electrical Stimulation. Semin Speech Lang. 2016;37(3):201-18.

11. Atkinson M, Kramer P, Wyman SM, Ingelfinger FJ. The dynamics of swallowing. I. Normal pharyngeal mechanisms. J Clin Invest. 1957;36(4):581-8.

12. Pandolfino JE, Kahrilas PJ. New technologies in the gastrointestinal clinic and research: impedance and high-resolution manometry. World J Gastroenterol. 2009;15(2):131-8.

13. van Hoeij FB, Bredenoord AJ. Clinical Application of Esophageal High-resolution Manometry in the Diagnosis of Esophageal Motility Disorders. J Neurogastroenterol Motil. 2016;22(1):6-13.

14. Bansal A, Kahrilas PJ. Has high-resolution manometry changed the approach to esophageal motility disorders? Current Opinion in Gastroenterology. 2010;26(4):344-51.

15. Savarino E, Marabotto E, Bodini G, Furnari M, Della Coletta M, Ghisa M, et al. Advancements in the use of manometry and impedance testing for esophageal functional disorders. Expert Rev Gastroenterol Hepatol. 2019;13(5):425-35.

16. Teitelbaum E, Dunst C. High-Resolution Esophageal Manometry: Techniques and Use in the Diagnosis of Esophageal Motility Disorders and for Surgical Decision Making. In: Yeo C, DeMeester S, McFadden D, Matthews J, Fleshman J, editors. Shackelford's Surgery of the Alimentary Tract. 2. 8th ed: Elsevier Inc; 2019. p. 115-28.

17. Herregods TV, Roman S, Kahrilas PJ, Smout AJ, Bredenoord AJ. Normative values in esophageal high-resolution manometry. Neurogastroenterol Motil. 2015;27(2):175-87.

18. Sweis R, Fox M. High-Resolution Manometry-Observations After 15 Years of Personal Use-Has Advancement Reached a Plateau? Curr Gastroenterol Rep. 2020;22(10):49.

19. Jones CA, Hoffman MR, Geng Z, Abdelhalim SM, Jiang JJ, McCulloch TM. Reliability of an automated high-resolution manometry analysis program across expert users, novice users, and speech-language pathologists. J Speech Lang Hear Res. 2014;57(3):831-6.

20. Takasaki K, Umeki H, Hara M, Kumagami H, Takahashi H. Influence of effortful swallow on pharyngeal pressure: evaluation using a high-resolution manometry. Otolaryngol Head Neck Surg. 2011;144(1):16-20.

21. Omari TI, Ciucci M, Gozdzikowska K, Hernandez E, Hutcheson K, Jones C, et al. High-Resolution Pharyngeal Manometry and Impedance: Protocols and Metrics-Recommendations of a High-Resolution Pharyngeal Manometry International Working Group. Dysphagia. 2019.

22. Rommel N, Hamdy S. Oropharyngeal dysphagia: manifestations and diagnosis. Nat Rev Gastroenterol Hepatol. 2016;13(1):49-59.

23. Fox MR, Bredenoord AJ. Oesophageal high-resolution manometry: moving from research into clinical practice. Gut. 2008;57(3):405-23.

24. Nunez L, Beamer S, Deussing L, Paul D, Aulbach S. Emerging Areas of Clinical Practice. American Speech-Language-Hearing Association; 2005.

25. Cichero J, Baldac S, Ledger M, Wilson C, Kaatzke-McDonald M, Agius E, et al. Dysphagia Clinical Guidelines. Australia: Speech Pathology Association of Australia Ltd; 2012.

26. Jones CA, Ciucci MR. Multimodal Swallowing Evaluation with High-Resolution Manometry Reveals Subtle Swallowing Changes in Early and Mid-Stage Parkinson Disease. J Parkinsons Dis. 2016;6(1):197-208.

27. Takasaki K, Umeki H, Enatsu K, Kumagami H, Takahashi H. Evaluation of swallowing pressure in a patient with amyotrophic lateral sclerosis before and after cricopharyngeal myotomy using high-resolution manometry system. Auris Nasus Larynx. 2010;37(5):644-7.

28. Schaen-Heacock NE, Jones CA, McCulloch TM. Pharyngeal Swallowing Pressures in Patients with Radiation-Associated Dysphagia. Dysphagia. 2020.

29. Omari TI, Kritas S, Cock C, Besanko L, Burgstad C, Thompson A, et al. Swallowing dysfunction in healthy older people using pharyngeal pressure-flow analysis. Neurogastroenterol Motil. 2014;26(1):59-68.

30. Hoffman MR, Mielens JD, Omari TI, Rommel N, Jiang JJ, McCulloch TM. Artificial neural network classification of pharyngeal high-resolution manometry with impedance data. Laryngoscope. 2013;123(3):713-20.

31. Nativ-Zeltzer N, Kahrilas PJ, Logemann JA. Manofluorography in the evaluation of oropharyngeal dysphagia. Dysphagia. 2012;27(2):151-61.

32. Jones CA, Forgues AL, Rogus-Pulia NM, Orne J, Macdonald CL, Connor NP, et al. Correlates of early pharyngeal high-resolution manometry adoption in expert speech-language pathologists. Dysphagia. 2019;34(3):325-32.

33. Jean A. Control of the central swallowing program by inputs from the peripheral receptors. A review. Journal of the Autonomic Nervous System. 1984;10:225-33.

34. Jean A. Brain Stem Control of Swallowing: Neuronal Network and Cellular Mechanisms. Physiological Reviews. 2001;81(2):929-69.

35. Aida S, Takeishi R, Magara J, Watanabe M, Ito K, Nakamura Y, et al. Peripheral and central control of swallowing initiation in healthy humans. Physiol Behav. 2015;151:404-11.

36. Matsuo K, Palmer J. Oral Phase Preparation and Propulsion: Anatomy, Physiology, Rheology, Mastication, and Transport. Principles of Deglutition2013. p. 117-31.

37. Sasegbon A, Hamdy S. The anatomy and physiology of normal and abnormal swallowing in

oropharyngeal dysphagia. Neurogastroenterol Motil. 2017;29(11).

38. Dodds WJ, Hogan WJ, Reid DP, Stewart ET, Arndorfer RC. A comparison between primary esophageal peristalsis following wet and dry swallows. Journal of Applied Physiology. 1973;35.

39. Miles A, Clark S, Jardine M, Allen J. Esophageal Swallowing Timing Measures in Healthy Adults During Videofluoroscopy. Ann Otol Rhinol Laryngol. 2016;125(9):764-9.

40. German RZ, Crompton AW, Gould FD, Thexton AJ. Animal Models for Dysphagia Studies: What Have We Learnt So Far. Dysphagia. 2017;32(1):73-7.

41. Ertekin C, Aydogdu I. Neurophysiology of swallowing. Clinical Neurophysiology. 2003;114(12):2226-44.

42. Palmer J. Electromyography of the muscles of oropharyngeal swallowing: basic concepts. Dysphagia. 1989;3:192-8.

43. Matsuo K, Palmer J. Anatomy and physiology of feeding and swallowing: normal and abnormal. Phys Med Rehabil Clin N Am. 2008;19(4):691-707, vii.

44. Miller AJ. Deglutition. Physiology & Behaviour. 1982;62(1):129-84.

45. Dodds WJ, Stewart ET, Logemann JA. Physiology and Radiology of the Normal Oral and Pharyngeal Phases of Swallowing. American Journal of Roentgenology 1990;154:953-63.

46. Zuercher P, Moret CS, Dziewas R, Schefold JC. Dysphagia in the intensive care unit: epidemiology, mechanisms, and clinical management. Crit Care. 2019;23(1):103.

47. Leopold NA, Kagel MC. Dysphagia-Ingestion or Deglutition?:A Proposed Paradigm. Dysphagia. 1997;12:202-6.

48. Steele CM, Miller AJ. Sensory input pathways and mechanisms in swallowing: a review. Dysphagia. 2010;25(4):323-33.

49. Atkinson M. Anatomy for Dental Students: Oxford University Press, Incorporated; 2013.

50. Logemann JA. Evaluation and Treatment of Swallowing Disorders: PRO_ED; 1998.

51. Shaw SM, Martino R. The normal swallow: muscular and neurophysiological control. Otolaryngol Clin North Am. 2013;46(6):937-56.

52. Yamada Y, Yamamura K, Inoue M. Coordination of cranial motoneurons during mastication. Respir Physiol Neurobiol. 2005;147(2-3):177-89.

53. Bojanowski V, Hummel T. Retronasal perception of odors. Physiol Behav. 2012;107(4):484-7.

54. Maeda K, Ono T, Otsuka R, Ishiwata Y, Kuroda T, Ohyama K. Modulation of Voluntary Swallowing by Visual Inputs in Humans. Dysphagia. 2004;19(1):1-6.

55. Moore KL, Dalley II AF, Agur AM. Clinically Oriented Anatomy, Seventh Edition. Philadelphia, PA: Lippincott Williams & Wilkins; 2014.

56. Leslie P, Hammond S. Scott-Brown's otorhinolaryngology, head and neck surgery. Gleeson M, editor1997.

57. Hiiemae KM, Palmer JB. Tongue Movements in Feeding and Speech. Critical Review Oral Biology Medicine. 2003;14(6):413-29.

58. Kieser JA, Farland MG, Jack H, Farella M, Wang Y, Rohrle O. The role of oral soft tissues in swallowing function: what can tongue pressure tell us? Aust Dent J. 2014;59 Suppl 1:155-61.

59. Schuenke M, Schulte E, Schumacher U. Thieme atlas of anatomy: neck and internal organs. . New York: Georg Thieme Verlag; 2010.

60. Leonard R, Kendall K. Dysphagia Assessment and Treatment Planning: A team approach - third edition. Leonard RJ, Kendall KA, editors. San Diego: Plural Publishing; 2014.

61. Kahrilas P, Lin S, Logemann J, Ergun G, Facchini F. Deglutitive Tongue action: Volume Accommodation and Bolus Propulsion. Gastroenterology. 1993;104:152-62.

62. Dantas R, Dodds E, Massey B, Shaker R, Cook I. Manometric Characteristics of Glossopalatal Sphincter. Dig Dis Sci. 1990;35(2):161-6.

63. Türker KS. Reflex Control of Human Jaw Muscles. Critical Review Oral Biology Medicine. 2002;13(1):85-104.

64. Jacobson S, Marcus EM. Neuroanatomy for the Neuroscientist. New York: Spinger; 2008.

65. Yamamura K, Kurose M, Okamoto K. Chemical Sensing Regulates Mastication/Swallowing. Current Pharmaceutical Design. 2016;22:2279-84.

66. Peyron MA, Mishellany A, Woda A. Particle Size Distribution of Food Boluses after Mastication of Six Natural Foods. Journal of Dental Research. 2004;83(7):578-82.

67. Pedersen A, Sorensen CE, Proctor GB, Carpenter GH. Salivary functions in mastication, taste and textural perception, swallowing and initial digestion. Oral Dis. 2018;24(8):1399-416.

68. Small DM. Flavor is in the brain. Physiol Behav. 2012;107(4):540-52.

69. Kennedy D, Kieser J, Bolter C, Swain M, Singh B, Waddell JN. Tongue pressure patterns during water swallowing. Dysphagia. 2010;25(1):11-9.

70. Palmer J. Bolus Aggregation in the Oropharynx Does Not Depend on Gravity. Arch Phys Med Rehabil. 1998;79:691-6.

71. Palmer J, Rudin N, Lara G, Crompton AW. Coordination of Mastication and Swallowing. Dysphagia. 1992;7:187-200.

72. Hiiemae KM, Palmer JB. Food Transport and Bolus Formation during Complete Feeding Sequences on Foods of Different Initial Consistency. Dysphagia. 1999;14:31-42.

73. Dua K, Ren J, Bardan E, Xie P, Shaker R. Coordination of Deglutitive Glottal Function and Pharyngeal Bolus Transit During Normal Eating. Gastroenterology. 1997;112:73-83.

74. Jennings CR. Surgical anatomy of the neck. . Scott-Brown's Otorhinolaryngology, Head and Neck Surgery. 2. 7th ed. London, England. : Hodder-Arnold; 1997. p. 1739-53.

75. Romanes GJ. Cunningham's Manual of Practical Anatomy. Oxford: Oxford Medical Publications; 2000.

76. Lang I. Brain stem control of the phases of swallowing. Dysphagia. 2009;24(3):333-48.

77. Belafsky P, Lintzenuch C, editors. Development, Anatomy, and Physiology of the Pharynx2013.

78. Donner M, Bosma J, Robertson D. Anatomy and Physiology of the Pharynx. Gastrointest Radiol. 1985;10:196-212.

79. Mittal RK, editor. Motor Function of the Pharynx, Esophagus, and its Sphincters: Morgan & Claypool Life Sciences; 2011.

80. Rosen SP, Jones CA, McCulloch TM. Pharyngeal swallowing pressures in the base-of-tongue and hypopharynx regions identified with three-dimensional manometry. Laryngoscope. 2017;127(9):1989-95.

81. Leonard RJ, Kendall KA, McKenzie S, Goncalves MI, Walker A. Structural displacements in normal swallowing: a videofluoroscopic study. Dysphagia. 2000;15(3):146-52.

82. Waqar M, Nawaz Abro M, Soomro Q, Shahban M, Khatoon S. Retrospective Incidence

Analysis of Head and Neck Cancer Patients in Rural Areas of Sindh, Pakistan. Jundishapur Journal of Chronic Disease Care. 2019;8(4).

83. Doty R, Bosma J. An electromyographic analysis of reflex deglutition. J Neurophysiol. 1956;19:44-60.

84. Lazarus C, Logemann J, Rademaker A, Kahrilas P, Pajak T, Lazar R, et al. Effects of Bolus Volume, Viscosity, and Repeated Swallows in Nonstroke Subjects and Stroke Patients. Arch Phys Med Rehabil. 1993;74:1066-70.

85. Ferris L, Schar M, McCall L, Doeltgen S, Scholten I, Rommel N, et al. Characterization of swallow modulation in response to bolus volume in healthy subjects accounting for catheter diameter. Laryngoscope. 2018;128(6):1328-34.

86. Miller AJ. Significance of Sensory Inflow To The Swallowing Reflex. Brain Research. 1972;43:147-59.

87. Alvarez-Berdugo D, Rofes, L, Arreola, V, Martin, A, Molina, L, Clave, P. A comparative study on the therapuetic effect of TRPV1, TRPA1, and TRPM8 agonists on swallowing dysfunction associated with aging and neurological diseases. Neurogastroenterol Motil. 2017.

88. Capra N, F. Mechanisms of Oral Sensation. Dysphagia. 1995;10:235-47.

89. Mansson I, Sandberg N. Salivary stimulus and swallowing reflex in man. Acta Otolaryngol. 1975;79(5-6):445-50.

90. Dua K, Surapaneni SN, Kuribayashi S, Hafeezullah M, Shaker R. Pharyngeal airway protective reflexes are triggered before the maximum volume of fluid that the hypopharynx can safely hold is exceeded. Am J Physiol Gastrointest Liver Physiol. 2011;301(2):G197-202.

91. Miller AJ. The neurobiology of swallowing and dysphagia. Dev Disabil Res Rev. 2008;14(2):77-86.

92. Mu LS, I. Sensory Nerve Supply of the Human Oro- and Laryngopharynx: A Preliminary Study. The Anatomical Record. 2000;258:406–20.

93. Stephen JR, Taves DH, Smith RC, Martin RE. Bolus location at the initiation of the pharyngeal stage of swallowing in healthy older adults. Dysphagia. 2005;20(4):266-72.

94. Steele CM, Peladeau-Pigeon M, Barbon CAE, Guida BT, Namasivayam-MacDonald AM, Nascimento WV, et al. Reference values for healthy swallowing across the range from thin to extremely thick liquids. J Speech Lang Hear Res. 2019;62(5):1338-63.

95. Bhutada AM, Dey R, Martin-Harris B, Focht Garand KL. Factors influencing initiation of pharyngeal swallow in healthy adults. Am J Speech Lang Pathol. 2020:1-9.

96. Martin-Harris B, Brodsky MB, Michel Y, Fu-Shing L, Walters B. Delayed Initiation of the Pharyngeal Swallow: Normal Variability in Adult Swallows. Journal of Speech, Language, and Hearing Research. 2007;50:585-94.

97. Saitoh E, Shibata S, Matsuo K, Baba M, Fujii W, Palmer JB. Chewing and food consistency: effects on bolus transport and swallow initiation. Dysphagia. 2007;22(2):100-7.

98. Ertekin C, Palmer JB. Physiology and electromyography of swallowing and its disorders. Prague, Czech Republic: 11th International Congress of Electromyography and Clinical Neurophysiology; 2000.

99. Mendell DA, Logemann JA. Temporal Sequence of Swallow Events During the Oropharyngeal Swallow. Journal of Speech, Language, and Hearing Research. 2007;50:1256-71.

100. Kendall KA, Leonard RJ, McKenzie SW. Sequence variability during hypopharyngeal bolus transit. Dysphagia. 2003;18(2):85-91.

101. Molfenter SM, Leigh C, Steele CM. Event sequence variability in healthy swallowing: building on previous findings. Dysphagia. 2014;29(2):234-42.

102. Kahrilas P, Lin S, Chen J, Logemann JA. Oropharyngeal Accommodation to Swallow Volume. Gastroenterology. 1996;111:297-306.

103. McConnell FM. Analysis of pressure generation and bolus transit during pharyngeal swallowing. Laryngoscope. 1988;98:71-8.

104. Cook I, Dodds W, Dantas R, Massey BT, Kern M, Lang I, et al. Opening mechanisms of the human upper esopahgeal sphincter. American Journal of Physiology. 1989;257(5):G748-G59.

105. May NH, Davidson KW, Pearson WG, Jr., O'Rourke AK. Pharyngeal swallowing mechanics associated with upper esophageal sphincter pressure wave. Head Neck. 2020;42(3):467-75.

106. Cock C, Jones CA, Hammer MJ, Omari TI, McCulloch TM. Modulation of Upper Esophageal Sphincter (UES) Relaxation and Opening During Volume Swallowing. Dysphagia. 2016;32(2):216-24.

107. Knigge MA, Thibeault S. Relationship Between Tongue Base Region Pressures and Vallecular Clearance. Dysphagia. 2016;31(3):391-7.

108. Palmer J, Tanaka E, Siebens A. Motions of the posterior pharyngeal wall in swallowing. Laryngoscope. 1988;98:414-7.

109. Kendall KA, McKenzie S, Leonard RJ, Goncalves MI, Walker A. Timing of events in normal swallowing: a videofluoroscopic study. Dysphagia. 2000;15(2):74-83.

110. Dua K, Shaker R, Ren J, Arndorfer R, Hofman C. Mechanism and timing of nasopharyngeak closure during swallowing and belching. Am J Physiol Gastro Liver Physiol. 1995;268:G1037-G42.

111. Gassert RB, Pearson WG, Jr. Evaluating muscles underlying tongue base retraction in deglutition using muscular functional magnetic resonance imaging (mfMRI). Magn Reson Imaging. 2016;34(2):204-8.

112. Pearson WG, Jr., Langmore SE, Yu LB, Zumwalt AC. Structural analysis of muscles elevating the hyolaryngeal complex. Dysphagia. 2012;27(4):445-51.

113. Thompson TZ, Obeidin F, Davidoff AA, Hightower CL, Johnson CZ, Rice SL, et al. Coordinate mapping of hyolaryngeal mechanics in swallowing. J Vis Exp. 2014(87).

114. Pearson WG, Jr., Langmore SE, Zumwalt AC. Evaluating the structural properties of suprahyoid muscles and their potential for moving the hyoid. Dysphagia. 2011;26(4):345-51.

115. Ishida R, Palmer J, Hiimemae K. Hyoid Motions During Swallowing: factors Affecting Forward and UPward Displacement. Dysphagia. 2002;17(4):262-72.

116. Dodds W, Man K, Cook I, Kahrilas P, Stewart E, Kern M. Influence of Bolus Volume on Swallow-Induced Hyoid Movement in Normal Subjects. American Journal of Reoentgenology. 1988;150:1307-9.

117. Nagy A, Molfenter SM, Peladeau-Pigeon M, Stokely S, Steele CM. The Effect of Bolus Consistency on Hyoid Velocity in Healthy Swallowing. Dysphagia. 2015;30(4):445-51.

118. Yokoyama M, Mitomi N, Tetsuka K, Tayama N, Niimi S. Role of Laryngeal Movement and Effect of Aging on Swallowing Pressure in the Pharynx and Upper Esophageal Sphincter. The Laryngoscope. 2000;110:434-9.

119. Cerenko D, McConnel FMS, Jackson RT. Quantitative assessment of pharyngeal bolus driving forces. Otolaryngol Head Neck Surg. 1989;100:57-63.

120. Sia I, Crary MA, Kairalla J, Carnaby GD, Sheplak M, McCulloch T. Derivation and

measurement consistency of a novel biofluid dynamics measure of deglutitive bolus-driving function-pharyngeal swallowing power. Neurogastroenterol Motil. 2019;31(1):e13465.

121. Walczak CC, Jones CA, McCulloch TM. Pharyngeal Pressure and Timing During Bolus Transit. Dysphagia. 2017;32(1):104-14.

122. Leonard R, Belafsky PC, Rees CJ. Relationship between fluoroscopic and manometric measures of pharyngeal constriction: The pharyngeal constriction ratio. Annals of Otology, Rhinology & Laryngology. 2006;115(2):897-901.

123. Gutierrez S, Iwanaga J, Pekala P, Yilmaz E, Clifton WE, Dumont AS, et al. The pharyngeal plexus: an anatomical review for better understanding postoperative dysphagia. Neurosurg Rev. 2020.

124. Miller AJ. Oral and Pharyngeal Reflexes In The Mammalian Nervous System: Their Diverse Range in Complexity And The Pivotal Role Of The Tongue. Crit Rev Oral Biol Med. 2002;13(5):409-25.

125. Bhatia SJ, Shah C. How to perform and interpret upper esophageal sphincter manometry. J Neurogastroenterol Motil. 2013;19(1):99-103.

126. Humbert IA, Poletto CJ, Saxon KG, Kearney PR, Crujido L, Wright-Harp W, et al. The effect of surface electrical stimulation on hyolaryngeal movement in normal individuals at rest and during swallowing. J Appl Physiol (1985). 2006;101(6):1657-63.

127. Logemann JA, Kahrilas PJ, Cheng J, Pauloski BR, Gibbons PJ, Rademaker AW, et al. Closure mechanisms of laryngeal vestibule during swallow. Am J Physiol Gastrointest Liver Physiol. 1992;262:G338-G44.

128. Vandeale D, Perlman A, Cassell M. Intrinsic fibre architecture and attachments of the human epiglottis and their contributions to the mechanism of deglutition. Journal of Anatomy. 1995;186:1-15.

129. Ekberg O. Closure of the Laryngeal Vestibule During Deglutition. Acta Oto-Laryngologica. 1982;93(1-6):123-9.

130. Foote AG, Thibeault SL. Sensory Innervation of the Larynx and the Search for Mucosal Mechanoreceptors. J Speech Lang Hear Res. 2021:1-21.

131. Vose A, Humbert I. “Hidden in Plain Sight”: A Descriptive Review of Laryngeal Vestibule Closure. Dysphagia. 2018;34(3):281-9.

132. Pearson WG, Jr., Taylor BK, Blair J, Martin-Harris B. Computational analysis of swallowing mechanics underlying impaired epiglottic inversion. Laryngoscope. 2016;126(8):1854-8.

133. Inamoto Y, Fujii N, Saitoh E, Baba M, Okada S, Katada K, et al. Evaluation of swallowing using 320-detector-row multislice CT. Part II: kinematic analysis of laryngeal closure during normal swallowing. Dysphagia. 2011;26(3):209-17.

134. Kidder T. Esophago/Pharyngo/Laryngeal Interrelationships: Airway Protection Mechanisms. Dysphagia. 1995;10:228-31.

135. Shaker R, Dodds W, Dantas R, Hogan WJ, Arndorfer RC. Coordination of deglutitive glottic closure with oropharyngeal swallowing. Gastroenterology. 1990;98:1478-84.

136. Shaker R, Dua KS, Ren J, Xie P, Funahashi A, Schapira RM. Vocal cord closure pressure during volitional swallow and other voluntary tasks. Dysphagia. 2002;17(1):13-8.

137. Martin-Harris B, Brodsky MB, Michel Y, Ford CL, Walters B, Heffner J. Breathing and Swallowing Dynamics Across the Adult Lifespan. Archives of Otolaryngology Head and Neck Surgery. 2005;131:762-70.

138. Martin-Harris B, Brodsky MB, Price CC, Michel Y, Walters B. Temporal coordination of

pharyngeal and laryngeal dynamics with breathing during swallowing: single liquid swallows. J Appl Physiol. 2003;94:1735-43.

139. Uysal H, Kizilay F, Unal A, Gungor HA, Ertekin C. The interaction between breathing and swallowing in healthy individuals. J Electromyogr Kinesiol. 2013;23(3):659-63.

140. Krishnan G, Goswami SP, Rangarathnam B. A Systematic Review of the Influence of Bolus Characteristics on Respiratory Measures in Healthy Swallowing. Dysphagia. 2020;35(6):883-97.

141. Pitts T, Rose MJ, Mortensen AN, Poliacek I, Sapienza CM, Lindsey BG, et al. Coordination of cough and swallow: a meta-behavioral response to aspiration. Respir Physiol Neurobiol. 2013;189(3):543-51.

142. Estis G, Ezri T, Tomori Z. Cough, expiration and aspiration reflexes: possible anesthetic implications - a brief review. Romanian Journal of Anaethesia and Intensive Care. 2014;21(2):113-7.

143. Steele CM, Grace-Martin K. Reflections on Clinical and Statistical Use of the Penetration-Aspiration Scale. Dysphagia. 2017;32(5):601-16.

144. Widdicombe J, Fontana G. Cough: what's in a name? Eur Respir J. 2006;28(1):10-5.

145. Ludlow C. Laryngeal Reflexes: Physiology, Technique, and Clinical Use. J Clin Neurophysiol. 2015;32:284-93.

146. Ebihara S, Izuukura H, Miyagi M, O'kuni I, Sekiya H, Ebihara T. Chemical Senses Affecting Cough and Swallowing. Current Pharmaceutical Design. 2016;22:2285-9.

147. Carey B, Sulica L, Wu A, Branski R. A novel electrodiagnostic assessment of the laryngeal closure reflex. Muscle Nerve. 2013;47(3):432-6.

148. Seikel JA, King DW, Drumright DG. Anatomy and physiology for speech, language and hearing second ed. San Diego, California. : Singular Publishing; 2000.

149. Amin MR, Belafsky PC. Cough and swallowing dysfunction. Otolaryngol Clin North Am. 2010;43(1):35-42, viii.

150. Kahrilas P, Dodds W, Dent J, Logemann J, Shaker R. Upper esophageal sphincter function during deglutition. Gastroenterology. 1988;95:52-62.

151. Goyal R, Martin S, Shapiro J, Spechler S. The role of cricopharyngeis muscle in pharyngoesophageal disorders. Dysphagia. 1993;8:252-8.

152. Jones CA, Hammer MJ, Hoffman MR, McCulloch TM. Quantifying contributions of the cricopharyngeus to upper esophageal sphincter pressure changes by means of intramuscular electromyography and high-resolution manometry. Ann Otol Rhinol Laryngol. 2014;123(3):174-82.

153. Kahrilas P, Dent J, Dodds W, Hogan W, Arndorfer R. A method for continuous monitoring of upper esophageal sphincter pressure. Digestive Diseases and Sciences. 1987;32(2):121-8.

154. Omari TI, Wiklendt L, Dinning P, Costa M, Rommel N, Cock C. Upper esophageal sphincter mechanical states analysis: a novel methodology to describe UES relaxation and opening. Front Syst Neurosci. 2014;8:241.

155. Lang I. Anatomy and physiology of the upper esophageal sphincter. The American Journal of Medicine. 1997;103(5):550S-55S.

156. Johnsson F, Shaw D, Gabb M, Dent J, Cook I. Influence of gravity and body position on normal oropharyngeal swallowing. Gastrointest Liver Physiol. 1995;32:G653-G8.

157. Singh S, Hamdy S. The upper oesophageal sphincter. Neurogastroenterol Motil. 2005;17:3-12.

158. Mason RJ, Bremner CG, DeMeester TR, Crookes PF, Peters JH, Hagen JA, et al.

Pharyngeal swallowing disorders selection for and outcome after myotomy. Annals of Surgery. 1998;228(4):598-607.

159. Dantas R, Kern M, Massey B, Dodds W, Kahrilas P, Brasseur J, et al. Effect of swallowed bolus variable on oral and pharyngeal phases of swallowing. Am J Physiol Gastrointest Liver Physiol. 1990;258:G675-81.

160. Jungheim M, Busche A, Miller S, Schilling N, Schmidt-Thieme L, Ptok M. Calculation of upper esophageal sphincter restitution time from high resolution manometry data using machine learning. Physiol Behav. 2016;165:413-24.

161. Sivaro D, Goyal RK. Functional Anatomy and Physiology of the Upper Esophageal Sphincter. Am J Med. 2000;108:27S-37S.

162. Omari TI, Jones CA, Hammer MJ, Cock C, Dinning P, Wiklendt L, et al. Predicting the activation states of the muscles governing upper esophageal sphincter relaxation and opening. Am J Physiol Gastrointest Liver Physiol. 2016;310(6):G359-66.

163. Jacob P, Kahrilas P, Logemann J, Shah V, Ha T. Upper esophageal sphincter opening and modulation during swallowing. Gastroenterology. 1989;97:1469-78.

164. Pouderoux P, Kahrilas PJ. Function of upper esophageal sphincter during swallowing: the grabbing effect. American journal of physiology : Gastrointestinal and liver physiology. 1997;272(5):G1057-G63.

165. Staller K, Kuo B. Development, Anatomy, and Physiology of the Esophagus. In: Shaker R, Belafsky PC, Postma GN, Easterling C, editors. Principles of Deglutition: A Multidisciplinary Text for Swallowing and it's Disorders. New York: Spinger Science+Business Media; 2013.

166. Hendrix T. Coordination of peristalsis in the pharynx and esophagus. Dysphagia. 1993;8:74-8.

167. Licht H, Fisher R. Downstream Effects of Esophageal Distension. Current Gastroenterology Reports. 2006;8:185-8.

168. Lang I, Medda B, Shaker R. Mechnisms of reflexes induced by esophageal distension. Am J Physiol Gastrointest Liver Physiol. 2001;281:G1246-G63.

169. Taniguchi H, Aoyagi Y, Matsuo K, Nakagawa K, Saitoh E. Development of an oesophageal stimulation method to elicit swallowing reflex in humans. J Oral Rehabil. 2018;45(3):211-5.

170. Woodland P, Sifrim D, Krarup AL, Brock C, Frokjaer JB, Lottrup C, et al. The neurophysiology of the esophagus. Ann N Y Acad Sci. 2013;1300:53-70.

171. Omari T, Kritas S, Cock C. New insights into pharyngo-esophageal bolus transport revealed by pressure-impedance measurement. Neurogastroenterology & Motility. 2012;24(11):e549-e56.

172. Hollenstein M, Thwaites P, Bütikofer S, Heinrich H, Sauter M, Ulmer I, et al. Pharyngeal swallowing and oesophageal motility during a solid meal test: a prospective study in healthy volunteers and patients with major motility disorders. The Lancet Gastroenterology & Hepatology. 2017;2(9):644-53.

173. O'Rourke A, Morgan LB, Coss-Adame E, Morrison M, Weinberger P, Postma G. The effect of voluntary pharyngeal swallowing maneuvers on esophageal swallowing physiology. Dysphagia. 2014;29(2):262-8.

174. Nekl CG, Lintzenich CR, Leng X, Lever T, Butler SG. Effects of effortful swallow on esophageal function in healthy adults. Neurogastroenterol Motil. 2012;24(3):252-6, e107-8.

175. Watts S, Gaziano J, Jacobs J, Richter J. Improving the Diagnostic Capability of the Modified Barium Swallow Study Through Standardization of an Esophageal Sweep Protocol. Dysphagia. 2019;34(1):34-42.

176. Michou E, Hamdy S. Cortical input in control of swallowing. Curr Opin Otolaryngol Head Neck Surg. 2009;17(3):166-71.

177. Clave P, Shaker R. Dysphagia: current reality and scope of the problem. Gastroenterology & Hepatology. 2015:259-70.

178. Mistry S, Hamdy S. Neural Control of Feeding and Swallowing. Physical Medicine and Rehabilitation Clinics of North America. 2008;19:709-28.

179. Alvarez-Berdugo, D R, Casamitjana JF, Padron A, Quer M, Clave P. Oropharyngeal and laryngeal sensory innervation in the pathophysiology of swallowing disorders and sensory stimulation treatments. Annals of The New York Academy of Sciences. 2018:104-20.

180. Sia I, Crary MA, Kairalla J, Carnaby GD, Sheplak M, McCulloch T. Bolus volume and viscosity effects on pharyngeal swallowing power-How physiological bolus accommodation affects bolus dynamics. Neurogastroenterol Motil. 2018;30(12):e13481.

181. Lowell SY, Poletto CJ, Knorr-Chung BR, Reynolds RC, Simonyan K, Ludlow CL. Sensory stimulation activates both motor and sensory components of the swallowing system. Neuroimage. 2008;42(1):285-95.

182. Regueiro M, Nascimento W, Parreira L, Dantas R. Videofluoroscopic analysis of different volumes of liquid bolus swallowing in healthy individuals: comparison between height and sex. Clinics. 2017;72(11):693-7.

183. Cook I, Dodds W, Dantas R, Kern M, Massey B, Shaker R, et al. Timing of Videofluoroscopic, Manometric Events, and Bolus Transit During the Oral and Pharyngeal Phases of Swallowing. Dysphagia. 1989:8-15.

184. Molfenter S, Steele C. Variation in Temporal Measures of Swallowing: Sex and Volume Effects. Dysphagia. 2012;28(2):226-33.

185. Nascimento WV, Cassiani RA, Santos CM, Dantas RO. Effect of bolus volume and consistency on swallowing events duration in healthy subjects. J Neurogastroenterol Motil. 2015;21(1):78-82.

186. Perlman A, Schultz J, VanDaele D. Effects of age, gender, bolus volume, and bolus viscosity on oropharyngeal pressure during swallowing. Journal of Applied Physiology. 1993;75(1):33-7.

187. Moon IY, Yi CH, Park IW, Yong JH. Effects of sitting posture and bolus volume on activation of swallowing-related muscles. J Oral Rehabil. 2020;47(5):577-83.

188. Steele CM, Peladeau-Pigeon M, Barbon CAE, Guida BT, Tapson MS, Valenzano TJ, et al. Modulation of Tongue Pressure According to Liquid Flow Properties in Healthy Swallowing. J Speech Lang Hear Res. 2019;62(1):22-33.

189. Shibata S, Inamoto Y, Saitoh E, Kagaya H, Aoyagi Y, Ota K, et al. The effect of bolus volume on laryngeal closure and UES opening in swallowing: Kinematic analysis using 320-row area detector CT study. J Oral Rehabil. 2017;44(12):974-81.

190. Lan Y, Xu GQ, Yu F, Lin T, Jiang LS, Liu F. The effect of bolus consistency on swallowing function measured by high-resolution manometry in healthy volunteers. Laryngoscope. 2017;127(1):173-8.

191. Butler SG, Postma GN, Fischer E. Effects of viscosity, taste, and bolus volume on swallowing apnea duration of normal adults. Otolaryngol Head Neck Surg. 2004;131(6):860-3.

192. Butler SG, Stuart A, Castell D, Russell GB, Koch K, Kemp S. Effects of age, gender, bolus condition, viscosity, and volume on pharyngeal and upper esophageal sphincter pressure and temporal measurements during swallowing. Journal of Speech, Language, and Hearing Research. 2009;52:240-53.

193. Smith LH, DeMyer WE. Anatomy of the brainstem. Seminars in Pediatric Neurology. 2003;10(4):235-40.

194. Costa MMB. Neural Control of Swallowing. Arq Gastroenterol. 2018;55Suppl 1(Suppl 1):61-75.

195. Kessler J, Jean A. Identification of the medullary swallowing regions in the rat. Exp Brain Res. 1985;57:256-63.

196. Bieger D. Rhombencephalic pathways and neurotransmitters controlling deglutition. American Journal of Medicine. 2001;111:85S-9S.

197. Thexton AJ, Crompton AW, German RZ. Electromyographic activity during the reflex pharyngeal swallow in the pig: Doty and Bosma (1956) revisited. J Appl Physiol (1985). 2007;102(2):587-600.

198. Amri. M., Car A, Jean A. Medullary Control of the Pontine Swallowing Neurones in Sheep. Exp Brain Res. 1984;55:105-10.

199. Doty R, Bosma J. An electromyographic analysis of reflex deglutition. Journal of Neurophysiology. 1956;19(1):44-60.

200. Doty RW. Influence of stimulus pattern on reflex deglutition. American Journal of Physiology. 1951;166(1):142-58.

201. Amirali A, Tsai G, Weisz D, SchrAder N, Sanders I. Mapping of brain stem neuronal circuitry active during swallowing. Ann Otol Rhinol Laryngol. 2001;110:502-13.

202. Lawton KJ, Perry WM, Yamaguchi A, Zornik E. Motor Neurons Tune Premotor Activity in a Vertebrate Central Pattern Generator. J Neurosci. 2017;37(12):3264-75.

203. Morquette P, Lavoie R, Fhima MD, Lamoureux X, Verdier D, Kolta A. Generation of the masticatory central pattern and its modulation by sensory feedback. Prog Neurobiol. 2012;96(3):340-55.

204. Gestreau C, Grelot L, Bianchi A. Activity of respiratory laryngeal motoneurons during fictive coughing and swallowing. Exp Brain Res. 2000;130:27-34.

205. Bautista T, Sun Q-J, Pilowsky P. The generation of pharyngeal phase of swallow and its coordination with breathing: Interaction between swallow and respiratory central pattern generators. Progress in Brain Research. 2014;212:253-75.

206. Chiao G, Larson C, Yajima Y, Ko P, Kahrilas PJ. Neuronal activity in nucleus ambiguous during deglutition and vocalisation in conscious monkeys. Exp Brain Res. 1994;100:29-38.

207. Doty R, Richmond W, Storey A. Effect of medullary lesions on coordination of deglutition. Experimental Neurology. 1967;17:91-106.

208. Cunningham E, Sawchenko P. Dorsal medullary pathways subserving oromotor reflexes in the rat: Implications for the central neuronal control of swallowing. The Journal of Comparative Neurology. 2000;417:448-66.

209. Amri M, Car A, Roman C. Axonal branching of medullary swallowing neurons projecting on the tirgeminal and hypoglossal motor nuclei: demonstration by electrophysiologocal and flurexcent double labeling techniques. Exp Brain Res. 1990;81:384-90.

210. Reed MD, English M, English C, Huff A, Poliacek I, Musselwhite MN, et al. The Role of the Cerebellum in Control of Swallow: Evidence of Inspiratory Activity During Swallow. Lung. 2019;197(2):235-40.

211. Flowers HL, Skoretz SA, Streiner DL, Silver FL, Martino R. MRI-based neuroanatomical predictors of dysphagia after acute ischemic stroke: a systematic review and meta-analysis. Cerebrovasc Dis. 2011;32(1):1-10.

212. Suzuki M, Asada Y, Ito J, Hayashi K, Inoue H, Kitano H. Activation of cerebellum and basal ganglia on volitional swallowing detected by functional magnetic resonance imaging. Dysphagia. 2003;18(2):71-7.

213. Hamdy S, Aziz Q, Rothwell JC, Singh KD, Barlow J, Hughes DG, et al. The cortical topography of human swallowing musculature in health and disease. Nature Medicine. 1996;2:1217-24.

214. Toogood JA, Smith RC, Stevens TK, Gati JS, Menon RS, Theurer J, et al. Swallowing Preparation and Execution: Insights from a Delayed-Response Functional Magnetic Resonance Imaging (fMRI) Study. Dysphagia. 2017;32(4):526-41.

215. Han DS, Chang YC, Lu CH, Wang TG. Comparison of disordered swallowing patterns in patients with recurrent cortical/subcortical stroke and first-time brainstem stroke. J Rehabil Med. 2005;37(3):189-91.

216. Mosier K, Bereznaya I. Parallel cortical networks for volitional control of swallowing in humans. Exp Brain Res. 2001;140(3):280-9.

217. Hamdy S, Rothwell JC, Brooks DJ, Bailey D, Aziz Q, Thompson DG. Identification of the Cerebral Loci Processing Human Swallowing With H 15O PET Activation. Journal of Neurophysiology. 1999;81:1917-26.

218. Martin RE, Goodyear BG, Gati JS, Menon RS. Cerebral Cortical Representation of Automatic and Volitional Swallowing in Humans. Journal of Neurophysiology. 2001;85(2):938-50.

219. Jestrović I, Coyle JL, Sejdić E. Decoding human swallowing via electroencephalography: a state-of-the-art review. Journal of Neural Engineering. 2015;12:1-15.

220. Alvar A, Hahn Arkenberg R, McGowan B, Cheng H, Malandraki GA. The Role of White Matter in the Neural Control of Swallowing: A Systematic Review. Front Hum Neurosci. 2021;15:628424.

221. Kern M, Jaradeh S, Arndorfer RC, Shaker R. Cerebral cortical representation of reflexive and volitional swallowing in humans. Am J Physiol Gastrointest Liver Physiol. 2001;280:G354-G60.

222. Yahagi R, Okuda-Akabaneb K, Fukamib H, Matsumotob N, Kitadab Y. Facilitation of voluntary swallowing by chemical stimulation of the posterior tongue and pharyngeal region in humans. Neuroscience Letters. 2008;448:139-42.

223. Nakamura Y, Hatakeyama A, Kitada Y, Tsujimura T, Taniguchi H, Inoue M. Effects of pharyngeal water stimulation on swallowing behaviors in healthy humans. Exp Brain Res. 2013;230(2):197-205.

224. Teismann IK, Steinstraeter O, Stoeckigt K, Suntrup S, Wollbrink A, Pantev C, et al. Functional oropharyngeal sensory disruption interferes with the cortical control of swallowing. BMC Neurosci. 2007;8:62.

225. Furlong PL, Hobson AR, Aziz Q, Barnes GR, Singh KD, Hillebrand A, et al. Dissociating the spatio-temporal characteristics of cortical neuronal activity associated with human volitional swallowing in the healthy adult brain. Neuroimage. 2004;22(4):1447-55.

226. Babaei A, Kern M, Antonik S, Mepani R, Ward BD, Li SJ, et al. Enhancing effects of flavored nutritive stimuli on cortical swallowing network activity. Am J Physiol Gastrointest Liver Physiol. 2010;299(2):G422-9.

227. Mistry S, Rothwell JC, Thompson DG, Hamdy S. Modulation of human cortical swallowing motor pathways after pleasant and aversive taste stimuli. Am J Physiol Gastrointest Liver Physiol. 2006;291(4):G666-71.

228. WHO. International Classification of Functioning, Disability and Health: ICF. Geneva, Switzerland: World Health Organization; 2001.

229. International Classification of Diseases (ICD-11) [Internet]. World Health Organization. 2018. Available from: https://icd.who.int/browse11/l-m/en

230. Rofes L, Arreola V, Almirall J, Cabre M, Campins L, Garcia-Peris P, et al. Diagnosis and management of oropharyngeal Dysphagia and its nutritional and respiratory complications in the elderly. Gastroenterol Res Pract. 2011;2011.

231. Simon SR, Pilz W, Hoebers FJP, Leeters IPM, Schols A, Willemsen ACH, et al. Malnutrition screening in head and neck cancer patients with oropharyngeal dysphagia. Clin Nutr ESPEN. 2021;44:348-55.

232. Almirall J, Rofes L, Serra-Prat M, Icart R, Palomera E, Arreola V, et al. Oropharyngeal dysphagia is a risk factor for community-acquired pneumonia in the elderly. Eur Respir J. 2013;41(4):923-8.

233. Reber E, Gomes F, Dahn IA, Vasiloglou MF, Stanga Z. Management of Dehydration in Patients Suffering Swallowing Difficulties. J Clin Med. 2019;8(11).

234. Namasivayam AM, Steele CM. Malnutrition and Dysphagia in long-term care: a systematic review. J Nutr Gerontol Geriatr. 2015;34(1):1-21.

235. DiBardino DM, Wunderink RG. Aspiration pneumonia: a review of modern trends. J Crit Care. 2015;30(1):40-8.

236. Baijens LW, Clave P, Cras P, Ekberg O, Forster A, Kolb GF, et al. European Society for Swallowing Disorders - European Union Geriatric Medicine Society white paper: oropharyngeal dysphagia as a geriatric syndrome. Clin Interv Aging. 2016;11:1403-28.

237. Threats TT. Use of the ICF in dysphagia management. Semin Speech Lang. 2007;28(4):323-33.

238. Allen J, Greene M, Sabido I, Stretton M, Miles A. Economic costs of dysphagia among hospitalized patients. Laryngoscope. 2020;130(4):974-9.

239. Jones E, Speyer R, Kertscher B, Denman D, Swan K, Cordier R. Health-Related Quality of Life and Oropharyngeal Dysphagia: A Systematic Review. Dysphagia. 2018;33(2):141-72.

240. Namasivayam-MacDonald AM, Shune SE. The influence of swallowing impairments as an independent risk factor for burden among caregivers of aging parents: A cross-sectional study. Geriatr Nurs. 2020;41(2):81-8.

241. Papadopoulos D, Bader I, Gkioxari E, Petta V, Tsaras T, Galanopoulou N, et al. Microbiology and prognosis assessment of hospitalized patients with aspiration pneumonia: a single- center prospective cohort study. Le Infezioni in Medicina. 2018;2:103-14,.

242. Ekberg O, Hamdy S, Woisard V, Wuttge-Hannig A, Ortega P. Social and psychological burden of dysphagia: its impact on diagnosis and treatment. Dysphagia. 2002;17(2):139-46.

243. Saito T, Hayashi K, Nakazawa H, Yagihashi F, Oikawa LO, Ota T. A Significant Association of Malnutrition with Dysphagia in Acute Patients. Dysphagia. 2018;33(2):258-65.

244. Westmark S, Melgaard D, Rethmeier LO, Ehlers LH. The cost of dysphagia in geriatric patients. ClinicoEconomics and Outcomes Research. 2018;Volume 10:321-6.

245. Kuhlemeier K. Epidemiology and Dysphagia. Dysphagia. 1994;9:209-17.

246. Allen J, Belafsky P. Symptom indices for dysphagia assessment and management. Principles of Deglutition: A multidisciplinary text for Swallowing and it's Disorders2013.

247. Bhutada AM, Broughton WA, Focht Garand KL. Obstructive sleep apnea syndrome (OSAS) and swallowing function-a systematic review. Sleep Breath. 2020.

248. Tang JA, Salapatas AM, Bonzelaar LB, Friedman M. Long-Term Incidence of

Velopharyngeal Insufficiency and Other Sequelae following Uvulopalatopharyngoplasty. Otolaryngol Head Neck Surg. 2017;156(4):606-10.

249. Franklin K, Anttila H, Axelsson S, Gislason T, Maasilta P, Nyhre K, et al. Effects and Side-Effects of Surgery for Snoring and Obstructive Sleep Apnea – A Systematic Review. Sleep. 2009;32(1):27-36.

250. McIntyre M, Doeltgen S, Dalton N, Koppa M, Chimunda T. Post-extubation dysphagia incidence in critically ill patients: A systematic review and meta-analysis. Aust Crit Care. 2020.

251. Brodsky MB, Nollet JL, Spronk PE, Gonzalez-Fernandez M. Prevalence, Pathophysiology, Diagnostic Modalities, and Treatment Options for Dysphagia in Critically Ill Patients. Am J Phys Med Rehabil. 2020;99(12):1164-70.

252. Hutcheson KA, Nurgalieva Z, Zhao H, Gunn GB, Giordano SH, Bhayani MK, et al. Two-year prevalence of dysphagia and related outcomes in head and neck cancer survivors: An updated SEER-Medicare analysis. Head Neck. 2019;41(2):479-87.

253. Arrese LC, Hutcheson K. Framework for speech-language pathology services in patients with oral cavity and oropharyngeal cancers. Oral and Maxillofacial Surgery Clinics of North America. 2018;30:397-410.

254. Francis D, Weymuller E, Parvathaneni U, Merati A, Yueh B. Dysphagia, Stricture, and Pneumonia in Head and Neck Cancer Patients: Does Treatment Modality Matter? Annals of Otology, Rhinology & Laryngology. 2010;119(6):391-7.

255. Epstein L, Kristo D, Strollo P, Friedman N, Malhotra A, Patil S, et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. Journal of Clinical Sleep Medicine. 2009;5(3):263-76.

256. Patil SP, Ayappa IA, Caples SM, Kimoff RJ, Patel SR, Harrod CG. Treatment of adult obstructive sleep apnea with positive airway pressure: an American academy of sleep medicine systematic review, meta-analysis, and GRADE Assessment. Journal of Clinical Sleep Medicine. 2019;15(02):301-34.

257. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med. 2002;165(9):1217-39.

258. Senaratna CV, Perret JL, Lodge CJ, Lowe AJ, Campbell BE, Matheson MC, et al. Prevalence of obstructive sleep apnea in the general population: A systematic review. Sleep Med Rev. 2017;34:70-81.

259. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurence of sleep-disordered breathing among middle-aged adults. The New England Journal of Medicine. 1993;328(17):1230-5.

260. Morley JE, Sanford A, Bourey R. Sleep apnea: A geriatric syndrome. JAMDA. 2017;18 899-904.

261. Chai-Coetzer C, -L., Antic NA, Rowland LS, Catcheside PG, Esterman A, Reed RL, et al. A simplified model of screening questionnaire and home monitoring for obstrcutive sleep apnea in primary care. Thorax. 2011;66:213-9.

262. Foundation SH. Asleep on the job: Costs of inadequate sleep in Australia. 2017.

263. Lang CJ, Appleton SL, Vakulin A, McEvoy RD, Vincent AD, Wittert GA, et al. Associations of undiagnosed obstructive sleep apnea and excessive daytime sleepiness with depression: An Australian population study. J Clin Sleep Med. 2017;13(4):575-82.

264. Gurpinar B, Friedman M, Senel GB, Sayin S, Boroosan A, Uyar Y, et al. Impact of upper airway collapse and sleep parameters on daytime sleepiness and sleep quality. Journal of Craniofacial Surgery. 2020;31(4):1026-9.

265. Traeger S, Reston J, Schoelles K, Phillips B. Obstructive sleep apnea and risk of motor vehicle crash: systematic review and meta-analysis. Journal of Clinical Sleep Medicine. 2009;5(6):573-81.

266. Bosi M, De Vito A, Eckert D, Steier J, Kotecha B, Vicini C, et al. Qualitative phenotyping of obstructive sleep apnea and its clinical usefulness for the sleep specialist. International Journal of Environmental Research and Public Health. 2020;17(6).

267. Ralls F, Cutchen L. A contemporary review of obstructive sleep apnea. Curr Opin Pulm Med. 2019;25(6):578-93.

268. Patel JA, Ray BJ, Fernandez-Salvador C, Gouveia C, Zaghi S, Camacho M. Neuromuscular function of the soft palate and uvula in snoring and obstructive sleep apnea: A systematic review. Am J Otolaryngol. 2018;39(3):327-37.

269. Rizzatti FG, Mazzotti DR, Mindel J, Maislin G, Keenan BT, Bittencourt L, et al. Defining Extreme Phenotypes of OSA Across International Sleep Centers. Chest. 2020;158(3):1187-97.

270. Saboisky JP, Butler JE, Gandevia SC, Eckert DJ. Functional role of neural injury in obstructive sleep apnea. Front Neurol. 2012;3:95.

271. Friberg D, Gazelius B, Lindblad LN, B. Habitual snorers and sleep apnoics have abnormal vascular reactions of the soft palatal mucosa on afferent nerve stimulation. The Laryngoscope. 1998;108:431-6.

272. Shah F, Holmlund T, Levring Jaghagen E, Berggren D, Franklin K, Forsgren S, et al. Axon and schwann cell degeneration in nerves of upper airway relates to pharyngeal dysfunction in snorers and patients with sleep apnea. Chest. 2018;154(5):1091-8.

273. Petrof BJ, Hendricks JC, Pack AI. Does Upper Airway Muscle Injury Trigger a Vicious Cycle in Obstructive Sleep Apnea? A Hypothesis. Sleep. 1996;19(6):465-71.

274. Valbuza JS, de Oliveira MM, Zancanella E, Conti CF, Prado LB, Carvalho LB, et al. Swallowing dysfunction related to obstructive sleep apnea: a nasal fibroscopy pilot study. Sleep Breath. 2011;15(2):209-13.

275. Levring Jaghagen E, Berggren D, Isberg A. Swallowing dysfunction related to snoring: A videoradiographic study. Acta Oto-Laryngologica. 2000;120:438-43.

276. Schindler A, Mozzanica F, Sonzini G, Plebani D, Urbani E, Pecis M, et al. Oropharyngeal dysphagia in patients with obstructive sleep apnea syndrome. Dysphagia. 2014;29(1):44-51.

277. Levring Jaghagen E, Franklin KA, Isberg A. Snoring, sleep apnoea and swallowing dysfunction: a videoradiographic study. Dentomaxillofac Radiol. 2003;32(5):311-6.

278. Jobin V, Champagne V, Beauregard J, Charbonneau I, McFarland DH, Kimoff RJ. Swallowing function and upper airway sensation in obstructive sleep apnea. Journal of Applied Physiology. 2007;102:1587-94.

279. Teramoto S, Sudo E, Matsuse T, Ohga E, Ishii T, Ouchi Y, et al. Impaired swallowing reflex in patients with obstructive sleep apnea syndrome. Chest. 1999;116(1):117-21.

280. Fujita S, Conway W, Zorick F, Roth T. Surgical correction of anatomic abnormalities in obstructive sleep apnea syndrome: uvulopalatopharyngoplasty. Otolaryngol Head Neck Surg. 1981;89(6):923-34.

281. MacKay S, Carney AS, Catcheside PG, Chai-Coetzer CL, Chia M, Cistulli PA, et al. Effect of Multilevel Upper Airway Surgery vs Medical Management on the Apnea-Hypopnea Index and Patient-Reported Daytime Sleepiness Among Patients With Moderate or Severe Obstructive Sleep Apnea: The SAMS Randomized Clinical Trial. JAMA. 2020.

282. Vicini C, Montevecchi F, Gobbi R, De Vito A, Meccariello G. Transoral robotic surgery for

obstructive sleep apnea syndrome: Principles and technique. World J Otorhinolaryngol Head Neck Surg. 2017;3(2):97-100.

283. Weaver TE, Grunstein RR. Adherence to continuous positive airway pressure therapy: the challenge to effective treatment. Proc Am Thorac Soc. 2008;5(2):173-8.

284. MacKay S, Lewis R, McEvoy D, Joosten S, Holt NR. Surgical management of obstructive sleep apnoea: A position statement of the Australasian Sleep Association. Respirology. 2020;25(12):1292-308.

285. Sawyer AM, Gooneratne NS, Marcus CL, Ofer D, Richards KC, Weaver TE. A systematic review of CPAP adherence across age groups: clinical and empiric insights for developing CPAP adherence interventions. Sleep Med Rev. 2011;15(6):343-56.

286. Meccariello G, Cammaroto G, Montevecchi F, Hoff PT, Spector ME, Negm H, et al. Transoral robotic surgery for the management of obstructive sleep apnea: a systematic review and meta-analysis. Eur Arch Otorhinolaryngol. 2017;274(2):647-53.

287. Kato MG, Isaac MJ, Gillespie MB, O'Rourke AK. The Incidence and Characterization of Globus Sensation, Dysphagia, and Odynophagia Following Surgery for Obstructive Sleep Apnea. J Clin Sleep Med. 2018;14(1):127-32.

288. MacKay S, Carney A, Woods C, Antic N, McEvoy R, Chia M, et al. Modified uvulopalatopharyngoplasty and coblation channeling of the tongue for obstructive sleep apnea: a multi-centre Australian trial. J Clin Sleep Med. 2013;9(2):117-24.

289. Eesa M, Montevecchi F, Hendawy E, D'Agostino G, Mecceriello G, Vicini C. Swallowing outcome after TORS for sleep apnea: short- and long-term evaluation. European Archives of Otorhinolaryngology. 2015;272:1537-41.

290. Corradi AMB, Valarelli LP, Grechi TH, Eckeli AL, Aragon DC, Kupper DS, et al. Swallowing evaluation after surgery for obstructive sleep apnea syndrome: uvulopalatopharyngoplasty vs. expansion pharyngoplasty. Eur Arch Otorhinolaryngol. 2018;275(4):1023-30.

291. Mesti J, Cahali MB. Evolution of swallowing in lateral pharyngoplasty with stylopharyngeal muscle preservation. Brazilian Journal of Otorhinolaryngology. 2012;78(6):51-5.

292. Zohar Y, Finkelstein Y, Strauss M, Ytshak S. Surgical Treatment of Obstructive Sleep Apnea. Archives of Otolaryngology Head and Neck Surgery. 1993;119:1023-9.

293. Hagert B, Wikbald K, Odkvist L, Wahren LK. Side Effects after Surgical Treatment of Snoring. Journal for Oto-Rhino-Laryngology and Its Related Specialties. 2000;62(2):76-80.

294. Levring Jaghagen E, Berggren D, Dahlqvist A, Isberg A. Prediction and risk of dysphagia after uvulopalatopharyngoplasty and uvulopalatoplasty. Acta Oto-Laryngologica. 2004;124:1197-203.

295. Levring Jaghagen E, Nilsson M, Isberg A. Persisting dysphagia after uvuolopalatoplasty performed with steel scalpal. The Laryngoscope. 1999;109:86-90.

296. Grontved AM, Karup P. Complaints and satisfaction after uvulopalatopharyngoplasty. Acta Otolaryngol Suppl. 2000;543:190-2.

297. Lysdahl M, Haraldsson PO. Uvulopalatopharyngoplasty Versus Laser Uvulopalatoplasty: Prospective Long-term Follow-up of Self-reported Symptoms. Acta Oto-Laryngologica. 2009;122(7):752-7.

298. Hultcrantz E, Johansson K, Bengtson H. The effect of uvulopalatopharyngoplasty without tonsillectomy using local anaesthesia: a prospective long-term follow-up. J Laryngol Otol. 1999;113(6):542-7.

299. Ferguson KA, Heighway K, Ruby RR. A randomized trial of laser-assisted uvulopalatoplasty

in the treatment of mild obstructive sleep apnea. Am J Respir Crit Care Med. 2003;167(1):15-9.

300. Goh YH, Mark I, Fee WE, Jr. Quality of life 17 to 20 years after uvulopalatopharyngoplasty. Laryngoscope. 2007;117(3):503-6.

301. Walker-Engstrom M-L, Tegelberg A, Wilhelsmsson B, Ringqvist I. 4-Year follow-up of treatment with dental appliance or uvulopa- latopharyngoplasty in patients with obstructive sleep apnea: a randomized study. Chest. 2002;121(3):739-46.

302. Aneeza W, Marina M, Razif M, Azimatun N, A. A, Sani A. Effects of uvulopalatopharyngoplasty: A seven year review. Medical Journal of Malaysia. 2011;66(2):129-32.

303. Haavisto L, Suonpaa J. Complications of uvulopalatopharyngoplasty. . Clin Otolaryngol Allied SCie. 1994;19:243-7.

304. Rombaux P, Hamoir M, Bertrand B, Aubert G, Liistro G, Rodenstein D. Postoperative Pain and Side Effects After Uvulopalatopharyngoplasty, Laser-Assisted Uvulopalatoplasty, and Radiofrequency Tissue Volume Reduction in Primary Snoring. Laryngoscope. 2003;113:2169-73.

305. Stuck BA, Maurer JT, Verse T, Hormann K. Tongue base reduction with temperature-controlled radiofrequency volumetric tissue reduction for treatment of obstructive sleep apnea syndrome. Acta Otolaryngol. 2002;122(5):531-6.

306. den Herder C, Kox D, van Tinteren H, de Vries N. Bipolar radiofrequency induced thermotherapy of the tongue base: Its complications, acceptance and effectiveness under local anesthesia. Eur Arch Otorhinolaryngol. 2006;263(11):1031-40.

307. Friedman M, H. I, Lowenthal S, Ramakrishnan V, Joseph N. Uvulopalatoplasty (UP2): A Modified Technique for Selected Patients. The Laryngoscope. 2004;114:441-9.

308. Lim DJ, Kang SH, Kim BH, Hong SC, Yu MS, Kim YH, et al. Treatment of obstructive sleep apnea syndrome using radiofrequency-assisted uvulopalatoplasty with tonsillectomy. Eur Arch Otorhinolaryngol. 2013;270(2):585-93.

309. Li KK, Powell NB, Riley RW, Guilleminault C. Temperature-controlled radiofrequency tongue base reduction for sleep-disordered breathing: Long-term outcomes. Otolaryngol Head Neck Surg. 2002;127(3):230-4.

310. Lundkvist K, Friberg D. Pharyngeal disturbances in OSAS patients before and 1 year after UPPP. Acta Otolaryngol. 2010;130(12):1399-405.

311. Neruntarat C. Genioglossus advancement and hyoid myotomy under local anaesthesia. Otolaryngology - Head and Neck Surgery. 2003;129(1):85-91.

312. Altman J, Halpert R, Mickelson S, Senior B. Effect of uvulopalatopharyngoplasty and genial and hyoid advancement on swallowing in patients with obstructive sleep apnea syndrome. Otolaryngology - Head and Neck Surgery. 1999;120(4):454-7.

313. Sorrenti G, Piccin O, Mondini S, Ceroni AR. One-phase management of severe obstructive sleep apnea: Tongue base reduction with hyoepiglottoplasty plus uvulopalatopharyngoplasty. Otolaryngology-Head and Neck Surgery. 2006;135:906-10.

314. Rohrer JW, Eller R, Santillan PG, Barrera JE. Geniotubercle Advancement With a Uvulopalatal Flap and Its Effect on Swallow Function in Obstructive Sleep Apnea. The Laryngoscope. 2014;125:758-61.

315. Ellis M, Pate M, Dorris H, Pearson WJ, Brown J. Computational analysis of swallowing mechanics after surgery for obstructive sleep apnea. Ears, Nose & Throat Journal. 2018;97(4-5):122-.

316. Mosier JM, Sakles JC, Law JA, Brown CA, 3rd, Brindley PG. Tracheal Intubation in the Critically Ill. Where We Came from and Where We Should Go. Am J Respir Crit Care Med.

2020;201(7):775-88.

317. Thomas EBM, Moss S. Tracheal intubation. Anaesthesia & Intensive Care Medicine. 2014;15(1):5-7.

318. Skoretz SA, Flowers HL, Martino R. The incidence of dysphagia following endotracheal intubation: a systematic review. Chest. 2010;137(3):665-73.

319. Malandraki GA, Markaki V, Georgopoulos VC, Psychogios L, Nanas S. Postextubation Dysphagia in Critical Patients: A First Report From the Largest Step-Down Intensive Care Unit in Greece. American Journal of Speech-Language Pathology. 2016;25:150-6.

320. Macht M, Wimbish T, Clark BJ, Benson AB, Burnham EL, Williams A, et al. Postextubation dysphagia is persistent and associated with poor outcomes in survivors of critical illness. Crit Care. 2011;15(5):R231.

321. Schefold JC, Berger D, Zurcher P, Lensch M, Perren A, Jakob SM, et al. Dysphagia in Mechanically Ventilated ICU Patients (DYnAMICS): A Prospective Observational Trial. Crit Care Med. 2017;45(12):2061-9.

322. Omura K, Komine A, Yanagigawa M, Chiba N, Osada M. Frequency and outcome of post-extubation dysphagia using nurse-performed swallowing screening protocol. Nurs Crit Care. 2019;24(2):70-5.

323. Barker J, Martino R, Reichardt B, Hickey EJ, Ralph-Edwards A. Incidence and impact of dysphagia in patients receiving prolonged endotracheal intubation after cardiac surgery. Canadian Journal fo Surgery. 2009;52:119-24.

324. Wunsch H, Angus DC, Harrison DA, Collange O, Fowler R, Hoste EA, et al. Variation in critical care services across North America and Western Europe. Crit Care Med. 2008;36(10):2787-93, e1-9.

325. Hicks P, Huckson S, Fenney E, Leggett I, Pilcher D, Litton E. The financial cost of intensive care in Australia: a multicentre registry study. Med J Aust. 2019;211(7):324-5.

326. Halpern NA, Pastores SM. Critical care medicine in the United States 2000-2005: an analysis of bed numbers, occupancy rates, payer mix, and costs. Crit Care Med. 2010;38(1):65-71.

327. Cuthberston B, Wunsch H. Long-Term Outcomes after Critical Illness The Best Predictor of the Future Is the Past. American Journal of Respiratory and Critical Care Medicine. 2016;194(2):132-3.

328. Park H, Koo J, Song S. Association of Post-extubation Dysphagia With Tongue Weakness and Somatosensory Disturbance in Non-neurologic Critically Ill Patients. Ann Rehabil Med. 2017;41(6):961-8.

329. Partik B, Pokieser P, Schim W, Schober E, Stadler A, Eisenhuber E, et al. Videofluoroscopy of Swallowing in Symptomatic Patients Who Have Undergone Long-Term Intubation. AJR. 2000;174:1409-12.

330. Scheel R, Pisegna JM, McNally E, Noordzij JP, Langmore SE. Endoscopic Assessment of Swallowing After Prolonged Intubation in the ICU setting. Annals of Otology, Rhinology & Laryngology. 2016;125(1):43-52.

331. Hafner G, Neuhuber A, Hirtenfelder S, Schmedler B, Eckel HE. Fiberoptic endoscopic evaluation of swallowing in intensive care unit patients. Eur Arch Otorhinolaryngol. 2008;265(4):441-6.

332. Krisciunas GP, Langmore SE, Gomez-Taborda S, Fink D, Levitt JE, McKeehan J, et al. The Association Between Endotracheal Tube Size and Aspiration (During Flexible Endoscopic Evaluation of Swallowing) in Acute Respiratory Failure Survivors. Crit Care Med. 2020;48(11):1604-11.

333. Brodsky MB, De I, Chilukuri K, Huang M, Palmer JB, Needham DM. Coordination of Pharyngeal and Laryngeal Swallowing Events During Single Liquid Swallows After Oral Endotracheal Intubation for Patients with Acute Respiratory Distress Syndrome. Dysphagia. 2018;33(6):768-77.

334. Skoretz SA, Yau TM, Granton JT, Martino R. The feasibility of assessing swallowing physiology following prolonged intubation after cardiovascular surgery. Pilot Feasibility Stud. 2017;3:62.

335. Kim MJ, Park YH, Park YS, Song YH. Associations Between Prolonged Intubation and Developing Post-extubation Dysphagia and Aspiration Pneumonia in Non-neurologic Critically Ill Patients. Ann Rehabil Med. 2015;39(5):763-71.

336. Brodsky MB, González-Fernández M, Mendez-Tellez PA, Shanholtz C, Palmer JB, Needham DM. Factors Associated with Swallowing Assessment after Oral Endotracheal Intubation and Mechanical Ventilation for Acute Lung Injury. Annals of the American Thoracic Society. 2014;11(10):1545-52.

337. Tolep K, Getch C, Criner G. Swallowing dysfunction in patients receiving prolonged mechanical ventilation. Chest. 1996;109(1):167+.

338. Marvin S, Thibeault S, Ehlenbach WJ. Post-extubation Dysphagia: Does Timing of Evaluation Matter? Dysphagia. 2019;34(2):210-9.

339. Nordally SO, Sohawpn S, DeGieter M, Bellout H, Verougstraete G. A study to determine the correlation between clinical, fibre-optic endoscopic evaluation of swallowing and videofluoroscopic evaluations of swallowing after prolonged intubation. Nutr Clin Pract. 2011;26(4):457-62.

340. El Solh A, Okada M, Bhat A, Pietrantoni C. Swallowing disorders post orotracheal intubation in the elderly. Intensive Care Med. 2003;29(9):1451-5.

341. Ajemian MS, Nirmul GB, Anderson MT, Zirlen DM, Kwasnik EM. Routine Fiberoptic Endoscopic Evaluation of Swallowing Following Prolonged Intubation. Archives of Surgery. 2001;136:434-7.

342. Barquist E, Brown E, Cohn S, Lundy D, Jackowski J. Postextubation fiberoptic endoscopic evaluation of swallowing after prolonged endotracheal intubation: A randomized, prospective trial. Critical Care Medicine. 2001;29(9):1710-3.

343. Leder SB, Cohn SM, B.A. M. Fiberoptic Endoscopic Documentation of the High Incidence of Aspiration following Extubation in Critically Ill Trauma Patients. Dysphagia. 1998;13:208-12.

344. Skoretz SA, Yau TM, Ivanov J, Granton JT, Martino R. Dysphagia and associated risk factors following extubation in cardiovascular surgical patients. Dysphagia. 2014;29(6):647-54.

345. Brown CV, Hejl K, Mandaville AD, Chaney PE, Stevenson G, Smith C. Swallowing dysfunction after mechanical ventilation in trauma patients. J Crit Care. 2011;26(1):108 e9-13.

346. Brodsky M, Gellar J, Dinglas V, Colantuoni E, Mendez-Tellez P, Shanholtz C, et al. Duration of oral endotracheal intubation is associated with dysphagia symptoms in acute lung injury patients. Journal of Critical Care. 2014;29:574-9.

347. Moraes DP, Sassi FC, Mangilli LD, Zilberstein B, de Andrade CR. Clinical prognostic indicators of dysphagia following prolonged orotracheal intubation in ICU patients. Crit Care. 2013;17(5):R243.

348. Brodsky MB, Huang M, Shanholtz C, Mendez-Tellez PA, Palmer JB, Colantuoni E, et al. Recovery from Dysphagia Symptoms after Oral Endotracheal Intubation in Acute Respiratory Distress Syndrome Survivors. A 5-Year Longitudinal Study. Ann Am Thorac Soc. 2017;14(3):376-83.

349. Macht M, Wimbish T, Bodine C, Moss M. ICU-acquired swallowing disorders. Crit Care

Med. 2013;41(10):2396-405.

350. Goldsmith T. Evaluation and treatment of swallowing disorders following endotracheal intubation and tracheostomy. Clinics. 2000;38:219-42.

351. Brodsky M, Levy M, Jedlanek E, Pandian V, Blackford B, Price C, et al. Laryngeal Injury and Upper Airway Symptoms After Oral Endotracheal Intubation With Mechanical Ventilation During Critical Care: A Systematic Review. Crit Care Med. 2018;46(12):2010-7.

352. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424.

353. Pezzuto F, Buonaguro L, Caponigro F, Ionna F, Starita N, Annunziata C, et al. Update on Head and Neck Cancer: Current Knowledge on Epidemiology, Risk Factors, Molecular Features and Novel Therapies. Oncology. 2015;89(3):125-36.

354. Chow LQM. Head and Neck Cancer. N Engl J Med. 2020;382(1):60-72.

355. Lubin JH, Purdue M, Kelsey K, Zhang ZF, Winn D, Wei Q, et al. Total exposure and exposure rate effects for alcohol and smoking and risk of head and neck cancer: a pooled analysis of case-control studies. Am J Epidemiol. 2009;170(8):937-47.

356. Chang ET, Adami HO. The enigmatic epidemiology of nasopharyngeal carcinoma. Cancer Epidemiol Biomarkers Prev. 2006;15(10):1765-77.

357. Mork J, Lie K, Glattre E, Hallmans G, Jellum E, Koskela P, et al. Human papillomavirus infection as a risk factor for squamous -cell carcinoma of the head and neck. New England Journal of Medicine. 2001;344(15):1125-31.

358. Tumban E. A Current Update on Human Papillomavirus-Associated Head and Neck Cancers. Viruses. 2019;11(10).

359. Zanoni DK, Patel SG, Shah JP. Changes in the 8th Edition of the American Joint Committee on Cancer (AJCC) Staging of Head and Neck Cancer: Rationale and Implications. Curr Oncol Rep. 2019;21(6):52.

360. Pfister DG, Spencer S, Adelstein D, Adkins D, Anzai Y, Brizel DM, et al. Head and Neck Cancers, Version 2.2020, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2020;18(7):873-98.

361. Johnson DE, Burtness B, Leemans CR, Lui VWY, Bauman JE, Grandis JR. Head and neck squamous cell carcinoma. Nat Rev Dis Primers. 2020;6(1):92.

362. Bernier J, Domenge C, Ozsahin M, Matuszewska K, Lefèbvre J-L, Greiner R, et al. Postoperative Irradiation with or without Concomitant Chemotherapy for Locally Advanced Head and Neck Cancer. The New England Journal of Medicine. 2004;350(19):1945-52.

363. Braakhuis BJ, Brakenhoff RH, Leemans CR. Treatment choice for locally advanced head and neck cancers on the basis of risk factors: biological risk factors. Ann Oncol. 2012;23 Suppl 10:x173-7.

364. Barton MB, Jacob S, Shafiq J, Wong K, Thompson SR, Hanna TP, et al. Estimating the demand for radiotherapy from the evidence: a review of changes from 2003 to 2012. Radiother Oncol. 2014;112(1):140-4.

365. Delaney GP, Barton MB. Evidence-based estimates of the demand for radiotherapy. Clin Oncol (R Coll Radiol). 2015;27(2):70-6.

366. Porto de Toledo I, Pantoja LLQ, Luchesi KF, Assad DX, De Luca Canto G, Guerra ENS. Deglutition disorders as a consequence of head and neck cancer therapies: a systematic review and meta-analysis. Support Care Cancer. 2019;27(10):3681-700.

367. Jiang N, Zhang LJ, Li LY, Zhao Y, Eisele DW. Risk factors for late dysphagia after (chemo)radiotherapy for head and neck cancer: A systematic methodological review. Head Neck. 2016;38(5):792-800.

368. Pauloski B, Rademaker A, Logemann J, Stein D, Beery Q, Newman L, et al. Pretreatment swallowing function in patients with head and neck cancer. Head & Neck. 2000;22(5):474-82.

369. van der Molen L, van Rossum MA, Ackerstaff AH, Smeele LE, Rasch CR, Hilgers FJ. Pretreatment organ function in patients with advanced head and neck cancer: clinical outcome measures and patients' views. BMC Ear Nose Throat Disord. 2009;9:10.

370. King SN, Dunlap NE, Tennant PA, Pitts T. Pathophysiology of Radiation-Induced Dysphagia in Head and Neck Cancer. Dysphagia. 2016;31(3):339-51.

371. Bentzen SM. Preventing or reducing late side effects of radiation therapy: radiobiology meets molecular pathology. Nat Rev Cancer. 2006;6(9):702-13.

372. Schindler A, Denaro N, Russi EG, Pizzorni N, Bossi P, Merlotti A, et al. Dysphagia in head and neck cancer patients treated with radiotherapy and systemic therapies: Literature review and consensus. Crit Rev Oncol Hematol. 2015;96(2):372-84.

373. Evangelista LM, Bayoumi A, Dyer BA, Shukla RP, Rao SD, Belafsky PC. The relationship between posterior pharyngeal wall thickness and swallowing function after radiation therapy. Acta Otolaryngol. 2020:1-4.

374. Hutcheson KA, Yuk MM, Holsinger FC, Gunn GB, Lewin JS, Irish J. Late radiation-associated dysphagia with lower cranial neuropathy in long-term oropharyngeal cancer survivors: Video case reports. Head & Neck. 2015;37(4):E56-E62.

375. Turcotte MC, Herzberg EG, Balou M, Molfenter SM. Analysis of pharyngeal edema post-chemoradiation for head and neck cancer: Impact on swallow function. Laryngoscope Investigative Otolaryngology. 2018;3(5):377-83.

376. Gawryszuk A, Bijl HP, Holwerda M, Halmos GB, Wedman J, Witjes MJH, et al. Functional Swallowing Units (FSUs) as organs-at-risk for radiotherapy. PART 1: Physiology and anatomy. Radiother Oncol. 2019;130:62-7.

377. Christianen ME, Langendijk JA, Westerlaan HE, van de Water TA, Bijl HP. Delineation of organs at risk involved in swallowing for radiotherapy treatment planning. Radiother Oncol. 2011;101(3):394-402.

378. Carmignani I, Locatello LG, Desideri I, Bonomo P, Olmetto E, Livi L, et al. Analysis of dysphagia in advanced-stage head-and-neck cancer patients: impact on quality of life and development of a preventive swallowing treatment. Eur Arch Otorhinolaryngol. 2018;275(8):2159-67.

379. Szczesniak MM, Maclean J, Zhang T, Graham PH, Cook IJ. Persistent dysphagia after head and neck radiotherapy: a common and under-reported complication with significant effect on non-cancer-related mortality. Clin Oncol (R Coll Radiol). 2014;26(11):697-703.

380. Wall LR, Ward EC, Cartmill B, Hill AJ. Physiological changes to the swallowing mechanism following (chemo)radiotherapy for head and neck cancer: a systematic review. Dysphagia. 2013;28(4):481-93.

381. Xinou E, Chryssogonidis I, Kalogera-Fountzila A, Panagiotopoulou-Mpoukla D, Printza A. Longitudinal Evaluation of Swallowing with Videofluoroscopy in Patients with Locally Advanced Head and Neck Cancer After Chemoradiation. Dysphagia. 2018;33(5):691-706.

382. Eisbruch A, Lyden T, Bradford CR, Dawson L, Haxer M, Miller A, et al. OBJECTIVE ASSESSMENT OF SWALLOWING DYSFUNCTION AND ASPIRATION AFTER RADIATION CONCURRENT WITH CHEMOTHERAPY FOR HEAD-AND-NECK CANCER. Int J Radiation

Oncology Biol Phys. 2002;53(1):23-8.

383. Kotz T, Costello R, Li Y, Posner MR. Swallowing dysfunction after chemoradiation for advanced squamous cell carcinoma of the head and neck. Head Neck. 2004;26(4):365-72.

384. Starmer HM, Tippett D, Webster K, Quon H, Jones B, Hardy S, et al. Swallowing outcomes in patients with oropharyngeal cancer undergoing organ-preservation treatment. Head Neck. 2014;36(10):1392-7.

385. Barbon CEA, Chepeha DB, Hope AJ, Peladeau-Pigeon M, Waito AA, Steele CM. Mechanisms of Impaired Swallowing on Thin Liquids Following Radiation Treatment for Oropharyngeal Cancer. J Speech Lang Hear Res. 2020:1-10.

386. Pauloski B, Rademaker A, Logemann J, Newman L, MacCracken E, Gaziano J, et al. Relationship between swallow motility disorders on videofluorography and oral intake in patients treated for head and neck cancer with radiotherapy with or without chemotherapy. Head Neck. 2006;28(12):1069-76.

387. Pauloski B, Rademaker A, Lazarus C, Boeckxstaens G, Kahrilas PJ, Logemann J. Relationship Between Manometric and Videofluoroscopic Measures of Swallow Function in Healthy Adults and Patients Treated for Head and Neck Cancer with Various Modalities. Dysphagia. 2008;24(2):196-203.

388. Logemann JA, Rademaker AW, Pauloski BR, Lazarus CL, Mittal BB, Brockstein B, et al. Site of disease and treatment protocol as correlates of swallowing function in patients with head and neck cancer treated with chemoradiation. Head Neck. 2006;28(1):64-73.

389. Florie M, Baijens L, Kremer B, Kross K, Lacko M, Verhees F, et al. Relationship between swallow-specific quality of life and fiber-optic endoscopic evaluation of swallowing findings in patients with head and neck cancer. Head Neck. 2016;38 Suppl 1:E1848-56.

390. Taylor-Goh S, editor. Royal College of Speech & Language Therapists Clinical Guidelines. 1st ed. London: Taylor & Francis Group; 2005.

391. Knowledge and skills needed by speech-language pathologists providing services to individuals with swallowing and/or feeding disorders [Internet]. 2002. Available from: www.asha.org/policy.

392. Preferred Practice Patterns for the Profession of Speech-Language Pathology. [Internet]. 2004. Available from: www.asha.org/policy.

393. Hollander-Mieritz C, Johansen J, Johansen C, Vogelius IR, Kristensen CA, Pappot H. Comparing the patients' subjective experiences of acute side effects during radiotherapy for head and neck cancer with four different patient-reported outcomes questionnaires. Acta Oncol. 2019;58(5):603-9.

394. Swan K, Cordier R, Brown T, Speyer R. Psychometric Properties of Visuoperceptual Measures of Videofluoroscopic and Fibre-Endoscopic Evaluations of Swallowing: A Systematic Review. Dysphagia. 2019;34(1):2-33.

395. Martino R, McCulloch T. Therapeutic intervention in oropharyngeal dysphagia. Nat Rev Gastroenterol Hepatol. 2016;13(11):665-79.

396. Brady S, Donzelli J. The modified barium swallow and the functional endoscopic evaluation of swallowing. Otolaryngol Clin North Am. 2013;46(6):1009-22.

397. Speyer R, Cordier R, Farneti D, Nascimento W, Pilz W, Verin E, et al. White Paper by the European Society for Swallowing Disorders: Screening and Non-instrumental Assessment for Dysphagia in Adults. Dysphagia. 2021.

398. Ghazanfar H, Shehi E, Makker J, Patel H. The Role of Imaging Modalities in Diagnosing Dysphagia: A Clinical Review. Cureus. 2021;13(7):e16786.

399. Patel DA, Sharda R, Hovis KL, Nichols EE, Sathe N, Penson DF, et al. Patient-reported outcome measures in dysphagia: a systematic review of instrument development and validation. Dis Esophagus. 2017;30(5):1-23.

400. Peng LC, Hui X, Cheng Z, Bowers MR, Moore J, Cecil E, et al. Prospective evaluation of patient reported swallow function with the Functional Assessment of Cancer Therapy (FACT), MD Anderson Dysphagia Inventory (MDADI) and the Sydney Swallow Questionnaire (SSQ) in head and neck cancer patients. Oral Oncol. 2018;84:25-30.

401. Garand KLF, McCullough G, Crary M, Arvedson JC, Dodrill P. Assessment Across the Life Span: The Clinical Swallow Evaluation. Am J Speech Lang Pathol. 2020;29(2S):919-33.

402. Dewan K, Clarke JO, Kamal AN, Nandwani M, Starmer HM. Patient Reported Outcomes and Objective Swallowing Assessments in a Multidisciplinary Dysphagia Clinic. Laryngoscope. 2021;131(5):1088-94.

403. Kirsh E, Naunheim M, Holman A, Kammer R, Varvares M, Goldsmith T. Patient-reported versus physiologic swallowing outcomes in patients with head and neck cancer after chemoradiation. Laryngoscope. 2019;129(9):2059-64.

404. van Hooren MRA, Vos R, Florie M, Pilz W, Kremer B, Baijens LWJ. Swallowing Assessment in Parkinson's Disease: Patient and Investigator Reported Outcome Measures are not Aligned. Dysphagia. 2021;36(5):864-74.

405. Florie M, Pilz W, Kremer B, Verhees F, Waltman G, Winkens B, et al. EAT-10 Scores and Fiberoptic Endoscopic Evaluation of Swallowing in Head and Neck Cancer Patients. Laryngoscope. 2020.

406. Belafsky P, Mouadeb D, Rees C, JC. P, Postma G, Allen J, et al. Validity and Reliability of the Eating Assessment Tool (EAT-10). Annals of Otology, Rhinology & Laryngology. 2008;117(2):919-24.

407. Carlozzi NE, Schilling S, Kratz AL, Paulsen JS, Frank S, Stout JC. Understanding patient-reported outcome measures in Huntington disease: at what point is cognitive impairment related to poor measurement reliability? Qual Life Res. 2018;27(10):2541-55.

408. Cohen ML, Hula WD. Patient-Reported Outcomes and Evidence-Based Practice in Speech-Language Pathology. Am J Speech Lang Pathol. 2020;29(1):357-70.

409. Felix CC, Joseph ME, Daniels SK. Clinical Decision Making in Patients with Stroke-Related Dysphagia. Semin Speech Lang. 2019;40(3):188-202.

410. Maccarini A, Filippin A, Padovani M, Limarzi M, Loffredo M, Casolino D. Clinical non-instrumental evaluation of dysphagia. Acta Otorhinolaryngol Ital. 2007;27:299-305.

411. Martino R, Pron G, Diamant NE. Oropharyngeal dysphagia: surveying practice patterns of the speech-language pathologist. Dysphagia. 2004;19(3):165-76.

412. Pettigrew CM, O'Toole C. Dysphagia evaluation practices of speech and language therapists in Ireland: clinical assessment and instrumental examination decision-making. Dysphagia. 2007;22(3):235-44.

413. Rumbach A, Coombes C, Doeltgen S. A Survey of Australian Dysphagia Practice Patterns. Dysphagia. 2018;33(2):216-26.

414. Rangarathnam B, McCullough GH. Utility of a Clinical Swallowing Exam for Understanding Swallowing Physiology. Dysphagia. 2016;31(4):491-7.

415. Smithard DG, O'Neill PA, Park CH, England R, Renwick DS, Wyatt R, et al. Can bedside assessment reliably exclude aspiration following acute stroke? Age and Ageing. 1998;27:99-106.

416. Lim SH, Lieu PK, Phua SY, Seshadri R, Venketasubramanian N, Lee SH, et al. Accuracy of

bedside clinical methods compared with fiberoptic endoscopic examination of swallowing (FEES) in determining the risk of aspiration in acute stroke patients. Dysphagia. 2001;16(1):1-6.

417. Linden P, Kuhlemeier K, Patterson C. The probability of correctly predicting subglottic penetration from clinical observations. Dysphagia. 1993;8(3):170-9.

418. Leder SB, Suiter DM, Murray J, Rademaker AW. Can an oral mechanism examination contribute to the assessment of odds of aspiration? Dysphagia. 2013;28(3):370-4.

419. Carnaby-Mann G, Lenius K. The bedside examination in dysphagia. Phys Med Rehabil Clin N Am. 2008;19:747-68.

420. González-Fernández M, Sein MT, Palmer JB. Clinical Experience Using the Mann Assessment of Swallowing Ability for Identification of Patients at Risk for Aspiration in a Mixed-Disease Population. American Journal of Speech-Language Pathology. 2011;20(4):331-6.

421. Im I, Carnaby GD, Takahashi N, Dungan S, Crary MA. Clinical Swallowing Profile Change in HNC Patients Treated with C/RT. Laryngoscope. 2021;131(6):E1873-E80.

422. Mitani Y, Oki Y, Fujimoto Y, Yamaguchi T, Yamada Y, Yamada K, et al. Relationship between the Functional Independence Measure and Mann Assessment of Swallowing Ability in hospitalized patients with pneumonia. Geriatr Gerontol Int. 2018;18(12):1620-4.

423. O'Horo JC, Rogus-Pulia N, Garcia-Arguello L, Robbins J, Safdar N. Bedside diagnosis of dysphagia: a systematic review. J Hosp Med. 2015;10(4):256-65.

424. Daniels SK, Brailey K, Priestly DH, Herrington LR, Weisberg LA, Foundas AL. Aspiration in Patients with Acute Stroke. Arch Phys Med Rehabil. 1998;19:14-9.

425. McCullough GH, Wertz RT, Rosenbek JC, Mills RH, Ross KB, Ashford JR. Inter- and intrajudge reliability of a clinical examination of swallowing in adults. Dysphagia. 2000;15(2):58-67.

426. Mathers-Schmidt BA, Kurlinski M. Dysphagia evaluation practices: inconsistencies in clinical assessment and instrumental examination decision-making. Dysphagia. 2003;18(2):114-25.

427. Bateman C, Leslie P, Drinnan MJ. Adult dysphagia assessment in the UK and Ireland: are SLTs assessing the same factors? Dysphagia. 2007;22(3):174-86.

428. Vogels B, Cartwright J, Cocks N. The bedside assessment practices of speech-language pathologists in adult dysphagia. Int J Speech Lang Pathol. 2015;17(4):390-400.

429. McAllister S, Kruger S, Doeltgen S, Tyler-Boltrek E. Implications of Variability in Clinical Bedside Swallowing Assessment Practices by Speech Language Pathologists. Dysphagia. 2016;31(5):650-62.

430. Pillay T, Pillay M. Contextualising clinical reasoning within the clinical swallow evaluation: A scoping review and expert consultation. S Afr J Commun Disord. 2021;68(1):e1-e12.

431. Langmore S, Aviv JE. Endoscopic Evaluation and Treatment of Swallowing Disorders Thieme; 2000.

432. Langmore SE, Schatz K, Olsen N. Fiberoptic Endoscopic Examination of Swallowing Safety: A New Procedure. Dysphagia. 1988;2:216-9.

433. Cimoli M, Holmes R, Lawson N, Rickardson K, Rowe J, Stanley C, et al. Clinical Guideline: Flexible Endoscopic Evaluation of Swallowing (FEES). 2019.

434. Kidder T, Langmore S, Martin B. Indications and Techniques of Endoscopy in Evaluation of Cervical Dysphagia: Comparisonwith Radiographic Techniques. Dysphaghia. 1994;9:256-61.

435. Aviv JE, Kaplan ST, Thomson JE, Spitzer J, Diamond B, Close LG. The safety of flexible endoscopic evaluation of swallowing with sensory testing (FEESST): an analysis of 500 consecutive evaluations. Dysphagia. 2000;15(1):39-44.

436. Miles A, Hunting A, McFarlane M, Caddy D, Scott S. Predictive Value of the New Zealand Secretion Scale (NZSS) for Pneumonia. Dysphagia. 2018;33(1):115-22.

437. Murray J, Langmore SE, Ginsberg S, Dostie A. The Significance of Accumulated Oropharyngeal Secretions and Swallowing Frequency in Predicting Aspiration. Dysphagia. 1996;11:99-103.

438. Marvin S, Gustafson S, Thibeault S. Detecting Aspiration and Penetration Using FEES With and Without Food Dye. Dysphagia. 2016;31(4):498-504.

439. Leder SB, Acton LM, Lisitano HL, Murray JT. Fiberoptic endoscopic evaluation of swallowing (FEES) with and without blue-dyed food. Dysphagia. 2005;20(2):157-62.

440. Curtis JA, Seikaly ZN, Dakin AE, Troche MS. Detection of Aspiration, Penetration, and Pharyngeal Residue During Flexible Endoscopic Evaluation of Swallowing (FEES): Comparing the Effects of Color, Coating, and Opacity. Dysphagia. 2020.

441. Langmore S. History of Fiberoptic Endoscopic Evaluation of Swallowing for Evaluation and Management of Pharyngeal Dysphagia: Changes over the Years. Dysphagia. 2017;32(1):27-38.

442. Leder SB, Novella S, Patwa H. Use of fiberoptic endoscopic evaluation of swallowing (FEES) in patients with amyotrophic lateral sclerosis. Dysphagia. 2004;19(3):177-81.

443. Matar N, Smaily H, Cherfane P, Hanna C. Profiling of Oropharyngeal Dysphagia in an Acute Care Hospital Setting. Ear Nose Throat J. 2021;100(8):NP357-NP61.

444. Kelly A, Leslie P, Beale T, Payten C, Drinnan M. Fibreoptic endoscopic evaluation of swallowing and videofluoroscopy: does examination type influence perception of pharyngeal residue severity? Clin Otolaryngol. 2006;31:425–32.

445. Kelly AM, Drinnan MJ, Leslie P. Assessing penetration and aspiration: how do videofluoroscopy and fiberoptic endoscopic evaluation of swallowing compare? Laryngoscope. 2007;117(10):1723-7.

446. Baijens LW, Speyer R, Pilz W, Roodenburg N. FEES protocol derived estimates of sensitivity: aspiration in dysphagic patients. Dysphagia. 2014;29(5):583-90.

447. Tohara H, Nakane A, Murata S, Mikushi S, Ouchi Y, Wakasugi Y, et al. Inter- and intra-rater reliability in fibroptic endoscopic evaluation of swallowing. J Oral Rehabil. 2010;37(12):884-91.

448. Prikladnicki A, Santana MG, Cardoso MC. Protocols and assessment procedures in fiberoptic endoscopic evaluation of swallowing: an updated systematic review. Braz J Otorhinolaryngol. 2021.

449. Leder S, Ross D, Briskin K, Sasaki CT. A prospective, double-blind randomized study on the use of a topical anesthetic, vasoconstritor, and placebo during transnasal flexible fibreoptic endoscopy. Journal of Speech, Language, and Hearing Research. 1997;40(6):1352-7.

450. Nacci A, Matteucci J, Romeo SO, Santopadre S, Cavaliere MD, Barillari MR, et al. Complications with Fiberoptic Endoscopic Evaluation of Swallowing in 2,820 Examinations. Folia Phoniatr Logop. 2016;68(1):37-45.

451. Pilz W, Vanbelle S, Kremer B, van Hooren MR, van Becelaere T, Roodenburg N, et al. Observers' Agreement on Measurements in Fiberoptic Endoscopic Evaluation of Swallowing. Dysphagia. 2016;31(2):180-7.

452. Badenduck LA, Matthews TW, McDonough A, Dort JC, Wiens K, Kettner R, et al. Fiber-optic endoscopic evaluation of swallowing to assess swallowing outcomes as a function of head position in a normal population. Journal of Otolaryngology - Head and Neck Surgery 2014;43(9).

453. Aghdam MA, Ogawa M, Iwahashi T, Hosokawa K, Kato C, Inohara H. A Comparison of Visual Recognition of the Laryngopharyngeal Structures Between High and Standard Frame Rate

Videos of the Fiberoptic Endoscopic Evaluation of Swallowing. Dysphagia. 2017;32(5):617-25.

454. Pisegna JM, Kaneoka A, Coster WJ, Leonard R, Langmore SE. Residue Ratings on FEES: Trends for Clinical Application of Residue Measurement. Dysphagia. 2020.

455. Rosenbek JC, Robbins JA, Roecker EB, Coyle JL, Wood JL. A penetration-aspiration scale. Dysphagia. 1996;11:93-8.

456. Butler S, Markley L, Sanders B, Stuart A. Reliability of the penetration aspiration scale with flexible endoscopic evaluation of swallowing. Ann Otol Rhinol Laryngol. 2015;124(6):480-3.

457. Neubauer PD, Rademaker AW, Leder SB. The Yale Pharyngeal Residue Severity Rating Scale: An Anatomically Defined and Image-Based Tool. Dysphagia. 2015;30(5):521-8.

458. Sabry A, Coyle JL, Abou-Elsaad T. Mansoura Fiberoptic Endoscopic Evaluation of Swallowing Residue Rating Scale (MFRRS): An Anatomically Based Tool - A Preliminary Study. Folia Phoniatr Logop. 2020:1-13.

459. Baijens L, Barikroo A, Pilz W. Intrarater and interrater reliability for measurements in videofluoroscopy of swallowing. Eur J Radiol. 2013;82(10):1683-95.

460. Jaffer NM, Ng E, Au FW, Steele CM. Fluoroscopic evaluation of oropharyngeal dysphagia: anatomic, technical, and common etiologic factors. AJR Am J Roentgenol. 2015;204(1):49-58.

461. Wolfram D, Attrill S, Baldac S, Ledger M, Wilson C, Burns C, et al. Clinical Guideline: Videofluoroscopic Swallow Study. 2013.

462. Martin-Harris B, Jones B. The videofluorographic swallowing study. Phys Med Rehabil Clin N Am. 2008;19(4):769-85, viii.

463. Lee JW, Randall DR, Evangelista LM, Kuhn MA, Belafsky PC. Subjective Assessment of Videofluoroscopic Swallow Studies. Otolaryngol Head Neck Surg. 2017;156(5):901-5.

464. Zammit-Maempel I, Chapple C-L, Leslie P. Radiation Dose in Videofluoroscopic Swallow Studies. Dysphagia. 2006;22(1):13-5.

465. Kim HM, Choi KH, Kim TW. Patients' radiation dose during videofluoroscopic swallowing studies according to underlying characteristics. Dysphagia. 2013;28(2):153-8.

466. ICRP. Radiological protection in medicine. ICRP Publication. 2007;37(2-4):9-34.

467. Bonilha HS, Huda W, Wilmskoetter J, Martin-Harris B, Tipnis SV. Radiation Risks to Adult Patients Undergoing Modified Barium Swallow Studies. Dysphagia. 2019.

468. Vose AK, Kesneck S, Sunday K, Plowman E, Humbert I. A Survey of Clinician Decision Making When Identifying Swallowing Impairments and Determining Treatment. J Speech Lang Hear Res. 2018;61(11):2735-56.

469. Scott A, Perry A, Bench J. A Study of Interrater Reliability when Using Videofluorscopy as an Assessment of Swallowing. Dysphagia. 1998;13:223-7.

470. McCullough GH, Wertz RT, Rosenbek JC, Mills RH, Webb WG, Ross KB. Inter- and Intrajudge Reliability for Videofluoroscopic Swallowing Evaluation Measures. Dysphagia. 2001;16:110-8.

471. Plowman EK, Humbert IA. Elucidating inconsistencies in dysphagia diagnostics: Redefining normal. Int J Speech Lang Pathol. 2018;20(3):310-7.

472. Pisegna JM, Langmore SE, Meyer TK, Pauloski B. Swallowing Patterns in the HNC Population: Timing of Penetration-Aspiration Events and Residue. Otolaryngol Head Neck Surg. 2020:194599820933883.

473. Martin-Harris B, Canon CL, Bonilha HS, Murray J, Davidson K, Lefton-Greif MA. Best Practices in Modified Barium Swallow Studies. Am J Speech Lang Pathol. 2020;29(2S):1078-93.

474. Bonilha HS, Humphries K, Blair J, Hill EG, McGrattan K, Carnes B, et al. Radiation exposure time during MBSS: influence of swallowing impairment severity, medical diagnosis, clinician experience, and standardized protocol use. Dysphagia. 2013;28(1):77-85.

475. Bonilha HS, Blair J, Carnes B, Huda W, Humphries K, McGrattan K, et al. Preliminary investigation of the effect of pulse rate on judgments of swallowing impairment and treatment recommendations. Dysphagia. 2013;28(4):528-38.

476. Schoeppe F, Sommer WH, Haack M, Havel M, Rheinwald M, Wechtenbruch J, et al. Structured reports of videofluoroscopic swallowing studies have the potential to improve overall report quality compared to free text reports. Eur Radiol. 2018;28(1):308-15.

477. Hazelwood RJ, Armeson KE, Hill EG, Bonilha HS, Martin-Harris B. Identification of Swallowing Tasks From a Modified Barium Swallow Study That Optimize the Detection of Physiological Impairment. J Speech Lang Hear Res. 2017;60(7):1855-63.

478. Mulheren RW, Azola A, Gonzalez-Fernandez M. Do Ratings of Swallowing Function Differ by Videofluoroscopic Rate? An Exploratory Analysis in Patients After Acute Stroke. Arch Phys Med Rehabil. 2019;100(6):1085-90.

479. Bryant KN, Finnegan E, Berbaum K. VFS interjudge reliability using a free and directed search. Dysphagia. 2012;27(1):53-63.

480. Nordin NA, Miles A, Allen J. Measuring Competency Development in Objective Evaluation of Videofluoroscopic Swallowing Studies. Dysphagia. 2017;32(3):427-36.

481. Martin-Harris B, Brodsky MB, Michel Y, Castell DO, Schleicher M, Sandidge J, et al. MBS measurement tool for swallow impairment--MBSImp: establishing a standard. Dysphagia. 2008;23(4):392-405.

482. Hutcheson KA, Barrow MP, Barringer DA, Knott JK, Lin HY, Weber RS, et al. Dynamic Imaging Grade of Swallowing Toxicity (DIGEST): Scale development and validation. Cancer. 2017;123(1):62-70.

483. Pearson WG, Jr., Molfenter SM, Smith ZM, Steele CM. Image-based measurement of post-swallow residue: the normalized residue ratio scale. Dysphagia. 2013;28(2):167-77.

484. Boaden E, Nightingale J, Bradbury C, Hives L, Georgiou R. Clinical practice guidelines for videofluoroscopic swallowing studies: A systematic review. Radiography (Lond). 2020;26(2):154-62.

485. Leder S, Murray JT. Fibreoptic endoscopic evaluation of swallowing. Phys Med Rehabil Clin N Am. 2008;19(4):787-801.

486. Fattori B, Giusti P, Mancini V, Grosso M, Barillari MR, Bastiani L, et al. Comparison between videofluoroscopy, fiberoptic endoscopy and scintigraphy for diagnosis of oro-pharyngeal dysphagia. Acta Otorhinolaryngol Ital. 2016;36(5):395-402.

487. Giraldo-Cadavid LF, Leal-Leano LR, Leon-Basantes GA, Bastidas AR, Garcia R, Ovalle S, et al. Accuracy of endoscopic and videofluoroscopic evaluations of swallowing for oropharyngeal dysphagia. Laryngoscope. 2017;127(9):2002-10.

488. Rao N, Brady S, Chaudhuri G, Donzelli J, Wesling M. Gold standard? Analysis of the videofluoroscopic and fibreoptic endoscopic swallow examinations

. Journal of Applied Research. 2003;3:89-96.

489. Yoon JA, Kim SH, Jang MH, Kim SD, Shin YB. Correlations between Aspiration and Pharyngeal Residue Scale Scores for Fiberoptic Endoscopic Evaluation and Videofluoroscopy. Yonsei Med J. 2019;60(12):1181-6.

490. Scharitzer M, Roesner I, Pokieser P, Weber M, Denk-Linnert DM. Simultaneous

Radiological and Fiberendoscopic Evaluation of Swallowing ("SIRFES") in Patients After Surgery of Oropharyngeal/Laryngeal Cancer and Postoperative Dysphagia. Dysphagia. 2019;34(6):852-61.

491. Pisegna JM, Langmore SE. Parameters of Instrumental Swallowing Evaluations: Describing a Diagnostic Dilemma. Dysphagia. 2016;31(3):462-72.

492. Hsiu C-H, Hasiao T-Y, Chen J-C, Chang Y-C, Lee S-Y. Evaluation of swallowing saftey with fiberoptic endoscope: Comparison with videofluorosopic technique. Laryngoscope. 1997;107:396-401.

493. Fox MR, Kahrilas PJ, Roman S, Gyawali CP, Scott SM, Rao SS, et al. Clinical measurement of gastrointestinal motility and function: who, when and which test? Nat Rev Gastroenterol Hepatol. 2018;15(9):568-79.

494. Cook IJ. Combined pharyngeal impedance-manometry: has it finally come of age? Clin Gastroenterol Hepatol. 2011;9(10):813-5.

495. Davidson K, O'Rourke A, Fortunato JE, Jadcherla S. The Emerging Importance of High-Resolution Manometry in the Evaluation and Treatment of Deglutition in Infants, Children, and Adults: New Opportunities for Speech-Language Pathologists. Am J Speech Lang Pathol. 2020;29(2S):945-55.

496. Knigge MA, Marvin S, Thibeault SL. Safety and Tolerability of Pharyngeal High-Resolution Manometry. Am J Speech Lang Pathol. 2019;28(1):43-52.

497. Cock C, Omari T. Diagnosis of Swallowing Disorders: How We Interpret Pharyngeal Manometry. Curr Gastroenterol Rep. 2017;19(3):11.

498. Szczesniak MM, Rommel N, Dinning PG, Fuentealba SE, Cook IJ, Omari TI. Intraluminal impedance detects failure of pharyngeal bolus clearance during swallowing: a validation study in adults with dysphagia. Neurogastroenterol Motil. 2009;21(3):244-52.

499. Omari TI, Rommel N, Szczesniak MM, Fuentealba S, Dinning PG, Davidson GP, et al. Assessment of intraluminal impedance for the detection of pharyngeal bolus flow during swallowing in healthy adults. Am J Physiol Gastrointest Liver Physiol. 2006;290(1):G183-8.

500. Omari T, Schar M. High-resolution manometry: what about the pharynx? Curr Opin Otolaryngol Head Neck Surg. 2018;26(6):382-91.

501. McConnel FMS, Cerenko D, Mendelsohn MS. Manofluorographic Analysis of Swallowing. Otolaryngol Clin North Am. 1988;21(4):625-35.

502. McConnel FMS, Cerenko D, Jackson RT, Hersh T. Clinical Application of the Manofluorogram. Laryngoscope. 1988:705-11.

503. Knigge MA, Thibeault S, McCulloch TM. Implementation of high-resolution manometry in the clinical practice of speech language pathology. Dysphagia. 2014;29(1):2-16.

504. Ryu JS, Park D, Oh Y, Lee ST, Kang JY. The Effects of Bolus Volume and Texture on Pharyngeal Pressure Events Using High-resolution Manometry and Its Comparison with Videofluoroscopic Swallowing Study. J Neurogastroenterol Motil. 2016;22(2):231-9.

505. Triggs J, Pandolfino J. Recent advances in dysphagia management. F1000Res. 2019;8.

506. Roman S, Huot L, Zerbib F, Bruley des Varannes S, Gourcerol G, Coffin B, et al. High-resolution manometry improves the diagnosis of esophageal motility disorders in patients with dysphagia: A randomized multicenter study. Am J Gastroenterol. 2016;111(3):372-80.

507. Pandolfino JE, Kahrilas PJ, American Gastroenterological A. AGA technical review on the clinical use of esophageal manometry. Gastroenterology. 2005;128(1):209-24.

508. Kahrilas PJ, Bredenoord AJ, Fox M, Gyawali CP, Roman S, Smout AJ, et al. The Chicago Classification of esophageal motility disorders, v3.0. Neurogastroenterol Motil. 2015;27(2):160-74.

509. Laing P, Bress AP, Fang J, Peterson K, Adler DG, Gawron AJ. Trends in diagnoses after implementation of the Chicago classification for esophageal motility disorders (V3.0) for high-resolution manometry studies. Dis Esophagus. 2017;30(12):1-6.

510. Yadlapati R, Pandolfino JE, Fox MR, Bredenoord AJ, Kahrilas PJ. What is new in Chicago Classification version 4.0? Neurogastroenterol Motil. 2021;33(1):e14053.

511. Gyawali CP, Sifrim D, Carlson DA, Hawn M, Katzka DA, Pandolfino JE, et al. Ineffective esophageal motility: Concepts, future directions, and conclusions from the Stanford 2018 symposium. Neurogastroenterol Motil. 2019;31(9):e13584.

512. Committee AT, Wang A, Pleskow DK, Banerjee S, Barth BA, Bhat YM, et al. Esophageal function testing. Gastrointest Endosc. 2012;76(2):231-43.

513. Robertson EV, Lee YY, Derakhshan MH, Wirz AA, Whiting JR, Seenan JP, et al. High-resolution esophageal manometry: addressing thermal drift of the manoscan system. Neurogastroenterol Motil. 2012;24(1):61-4, e11.

514. Lamvik K, Guiu Hernandez E, Jones R, Huckabee ML. Characterization and correction of pressure drift in the ManoScan() high-resolution manometry system: In vitro and in vivo. Neurogastroenterol Motil. 2016;28(5):732-42.

515. Babaei A, Lin EC, Szabo A, Massey BT. Determinants of pressure drift in Manoscan esophageal high-resolution manometry system. Neurogastroenterol Motil. 2015;27(2):277-84.

516. Robbins J, Hamilton J, Lof G, Kempster G. Oropharyngeal swallowing in normal adults of different ages. Gastroenterology. 1992;103:823-9.

517. Huggins P, Tuomi S, Young C. Effect of nasogastric tubes on the young, nomral swallowing mechanism. Dysphagia. 1999;14:157-61.

518. Guiu Hernandez E, Gozdzikowska K, Apperley O, Huckabee ML. Effect of topical nasal anesthetic on swallowing in healthy adults: A double-blind, high-resolution manometry study. Laryngoscope. 2018;128(6):1335-9.

519. Mesures BIdPe. The International Systems of Units (SI). Organisation Intergouvernementale de la Convention du Mètre; 2006.

520. Kahrilas PJ, Clouse RE, Hogan WJ. American Gastroenterological Association technical review on the clinical use of esophageal manometry. Gastroenterology. 1994;107:1865-84.

521. Bredenoord A, Hebbard G. Technical aspects of clinical high-resolution manometry studies. Neurogastroenterol Motil. 2012;24:5-10.

522. Kessing BF, Weijenborg PW, Smout AJ, Hillenius S, Bredenoord AJ. Water-perfused esophageal high-resolution manometry: normal values and validation. Am J Physiol Gastrointest Liver Physiol. 2014;306(6):G491-5.

523. Dodds WJ, Hogan WJ, Lydon SB, Stewart ET, Stef JJ, Arndorfer RC. Quantification of pharyngeal motor function in normal human subjects. Journal of Applied Physiology. 1975;39(4):692-6.

524. Evaluation of Gastrointestinal Motility and its Disorders. Ghoshal U, editor. India: Spinger; 2016.

525. Jones CA, Ciucci MR, Hammer MJ, McCulloch TM. A multisensor approach to improve manometric analysis of the upper esophageal sphincter. Laryngoscope. 2016;126(3):657-64.

526. Masuda T, Yano F, Omura N, Tsuboi K, Hoshino M, Yamamoto S, et al. Optimal cutoff value of integrated relaxation pressure on the esophagogastric junction to detect outflow obstruction using starlet high-resolution manometry system. J Gastroenterol. 2021;56(3):231-9.

527. Grübel C, Hiscock R, Hebbard G. Value of Spatiotemporal Representation of Manometric

Data. Clinical Gastroenterology and Hepatology. 2008;6(5):525-30.

528. Takasaki K, Umeki H, Enatsu K, Tanaka F, Sakihama N, Kumagami H, et al. Investigation of pharyngeal swallowing function using high-resolution manometry. Laryngoscope. 2008;118(10):1729-32.

529. Rice TW, Shay SS. A primer of high-resolution esophageal manometry. Semin Thorac Cardiovasc Surg. 2011;23(3):181-90.

530. Fattal M, Suiter DM, Warner HL, Leder SB. Effect of presence/absence of a nasogastric tube in the same person on incidence of aspiration. Otolaryngol Head Neck Surg. 2011;145(5):796-800.

531. Kim G, Baek S, Park HW, Kang EK, Lee G. Effect of Nasogastric Tube on Aspiration Risk: Results from 147 Patients with Dysphagia and Literature Review. Dysphagia. 2018;33(6):731-8.

532. Leder SB, Suiter DM. Effect of nasogastric tubes on incidence of aspiration. Arch Phys Med Rehabil. 2008;89(4):648-51.

533. Wang ZY, Chen JM, Ni GX. Effect of an indwelling nasogastric tube on swallowing function in elderly post-stroke dysphagia patients with long-term nasal feeding. BMC Neurol. 2019;19(1):83.

534. Pryor LN, Ward EC, Cornwell PL, O'Connor SN, Finnis ME, Chapman MJ. Impact of nasogastric tubes on swallowing physiology in older, healthy subjects: A randomized controlled crossover trial. Clin Nutr. 2015;34(4):572-8.

535. Lester S, Langmore SE, Lintzenich CR, Wright SC, Grace-Martin K, Fife T, et al. The effects of topical anesthetic on swallowing during nasoendoscopy. Laryngoscope. 2013;123(7):1704-8.

536. Sunkaraneni VS, Jones SE. Topical anaesthetic or vasoconstrictor preparations for flexible fibre-optic nasal pharyngoscopy and laryngoscopy. Cochrane Database Syst Rev. 2011(3):CD005606.

537. O'Dea MB, Langmore SE, Krisciunas GP, Walsh M, Zanchetti LL, Scheel R, et al. Effect of Lidocaine on Swallowing During FEES in Patients With Dysphagia. Ann Otol Rhinol Laryngol. 2015;124(7):537-44.

538. Jungheim M, Schubert C, Miller S, Ptok M. Swallowing Function After Continuous Neuromuscular Electrical Stimulation of the Submandibular Region Evaluated by High-Resolution Manometry. Dysphagia. 2017;32(4):501-8.

539. Jungheim M, Janhsen AM, Miller S, Ptok M. Impact of neuromuscular electrical stimulation on upper esophageal sphincter dynamics: a high-resolution manometry study. Ann Otol Rhinol Laryngol. 2015;124(1):5-12.

540. Hernandez J, Leverson G, Thibeault S. Effect of Lidocaine on Comfort and Swallowing Pressures During Pharyngeal High-Resolution Manometry. Dysphagia. 2021;36(3):439-42.

541. Ertekin C, Kiylioglu N, Tarlaci S, Keskin A, Aydogdu I. Effect of mucosal anaesthesia on oropharyngeal swallowing. Neurogastroenterol Motil. 2000;12:567-72.

542. Kamarunas EE, McCullough GH, Guidry TJ, Mennemeier M, Schluterman K. Effects of topical nasal anesthetic on fiberoptic endoscopic examination of swallowing with sensory testing (FEESST). Dysphagia. 2014;29(1):33-43.

543. Fife TA, Butler SG, Langmore SE, Lester S, Wright SC, Jr., Kemp S, et al. Use of topical nasal anesthesia during flexible endoscopic evaluation of swallowing in dysphagic patients. Ann Otol Rhinol Laryngol. 2015;124(3):206-11.

544. Ferris L, Doeltgen S, Cock C, Rommel N, Schar M, S. Cn, et al. Modulation of pharyngeal swallowing by bolus volume and viscosity. American Journal of Physiology-Gastrointestinal and Liver Physiology. 2020.

545. Burton MJ, Altman KW, Rosenfeld RM. Extracts from The Cochrane Library: Topical anaesthetic or vasoconstrictor preparations for flexible fibre-optic nasal pharyngoscopy and laryngoscopy. Otolaryngol Head Neck Surg. 2012;146(5):694-7.

546. Johnson PE, Belafsky PC, Postma G. Topical nasal anesthesia and laryngopharyngeal snesory testing: A prospective, double-blind crossover study. Ann Otol Rhinol Laryngol. 2003;112:14-6.

547. Kahrilas P, Ghosh S, Pandolfino J. Esophageal Motility Disorders in Terms of Pressure Topography The Chicago Classification. J Clin Gastroenterol. 2008;42(5):627-35.

548. Clouse R, Staiano A, Alrakawi A, Haroian L. Application of Topographical Methods to Clinical Esophageal Manometry. The American Journal of Gastroenterology. 2000;95(10):2720-30.

549. Takasaki K, Umeki H, Kumagami H, Takahashi H. Influence of head rotation on upper esophageal sphincter pressure evaluated by high-resolution manometry system. Otolaryngol Head Neck Surg. 2010;142(2):214-7.

550. Lin T, Xu G, Dou Z, Lan Y, Yu F, Jiang L. Effect of bolus volume on pharyngeal swallowing assessed by high-resolution manometry. Physiol Behav. 2014;128:46-51.

551. McCulloch TM, Hoffman MR, Ciucci M. High-resolution manometry of pharyngeal swallow pressure events associated with head turn and chin tuck. The Annals of Otology, Rhinology & Laryngology. 2010;119(6):369-76.

552. Hoffman MR, Mielens JD, Ciucci MR, Jones CA, Jiang JJ, McCulloch TM. High-resolution manometry of pharyngeal swallow pressure events associated with effortful swallow and the Mendelsohn maneuver. Dysphagia. 2012;27(3):418-26.

553. Nativ-Zeltzer N, Logemann JA, Zecker SG, Kahrilas PJ. Pressure topography metrics for high-resolution pharyngeal-esophageal manofluorography-a normative study of younger and older adults. Neurogastroenterol Motil. 2016;28(5):721-31.

554. Mielens JD, Hoffman MR, Ciucci MR, McCulloch TM, Jiang JJ. Application of Classification Models to Pharyngeal High-Resolution Manometry. Journal of Speech, Language, and Hearing Research. 2012;55(3):892-902.

555. Nguyen H, Domingues G, Lammert F. Technological insights: combined impedance manometry for esophageal motility testing-current results and further implications. World J Gastroenterol. 2006;12(39):6266-73.

556. Dinning PG, Arkwright JW, Gregersen H, O'Grady G, Scott SM. Technical advances in monitoring human motility patterns. Neurogastroenterol Motil. 2010;22(4):366-80.

557. Kahrilas PJ, Sifrim D. High-resolution manometry and impedance-pH/manometry: valuable tools in clinical and investigational esophagology. Gastroenterology. 2008;135(3):756-69.

558. Lee TH, Lee JS, Kim WJ. High resolution impedance manometric findings in dysphagia of Huntington's disease. World J Gastroenterol. 2012;18(14):1695-9.

559. Fass J, Silny J, Braun J, Heindrichs U, Dreuw B, Schumpelick V, et al. Measuring esophageal motility with a new intraluminal impedance device. First clinical results in reflux patients. Scand J Gastroenterol. 1994;29(8):693-702.

560. Nguyen H, Silny J, Matern S. Multiple Intraluminal Electrical Impedancometry for Recording of Upper Gastrointestinal Motility: Current Results and Further Implications. The American Journal of Gastroenterology. 1999;94(2):306-17.

561. Szczesniak MM, Wu PI, Maclean J, Omari TI, Cook IJ. The critical importance of pharyngeal contractile forces on the validity of intrabolus pressure as a predictor of impaired pharyngo-esophageal junction compliance. Neurogastroenterol Motil. 2018;30(10):e13374.

562. Szczesniak MM, Rommel N, Dinning PG, Fuentealba SE, Cook IJ, Omari TI. Optimal criteria for detecting bolus passage across the pharyngo-oesophageal segment during the normal swallow using intraluminal impedance recording. Neurogastroenterol Motil. 2008;20(5):440-7.

563. Lee TH, Lee JS, Park JW, Cho SJ, Hong SJ, Jeon SR, et al. High-resolution impedance manometry facilitates assessment of pharyngeal residue and oropharyngeal dysphagic mechanisms. Dis Esophagus. 2014;27(3):220-9.

564. Park EJ, Lee JS, Lee TH, Bok GH, Hong SJ, Kim HG, et al. High-resolution Impedance Manometry Criteria in the Sitting Position Indicative of Incomplete Bolus Clearance. J Neurogastroenterol Motil. 2014;20(4):491-6.

565. Noll L, Rommel N, Davidson GP, Omari TI. Pharyngeal flow interval: a novel impedance-based parameter correlating with aspiration. Neurogastroenterology & Motility. 2011;23(6):551-e206.

566. Kritas S, Dejaeger E, Tack J, Omari T, Rommel N. Objective prediction of pharyngeal swallow dysfunction in dysphagia through artificial neural network modeling. Neurogastroenterol Motil. 2016;28(3):336-44.

567. Omari TI, Dejaeger E, van Beckevoort D, Goeleven A, Davidson GP, Dent J, et al. A method to objectively assess swallow function in adults with suspected aspiration. Gastroenterology. 2011;140(5):1454-63.

568. Mielens JD, Hoffman MR, Ciucci MR, Jiang JJ, McCulloch TM. Automated analysis of pharyngeal pressure data obtained with high-resolution manometry. Dysphagia. 2011;26(1):3-12.

569. Omari TI, Dejaeger E, Van Beckevoort D, Goeleven A, De Cock P, Hoffman I, et al. A novel method for the nonradiological assessment of ineffective swallowing. Am J Gastroenterol. 2011;106(10):1796-802.

570. The MathWorks I. MATLAB Program. Natick, MA.

571. Singendonk M, Cock C, Bieckmann L, Szczesniak M, Ferris L, Benninga M, et al. Reliability of an online analysis platform for pharyngeal high-resolution impedance manometry recordings. Speech, Language and Hearing. 2018;22(4):195-203.

572. Szczesniak MM, Maclean J, Zhang T, Liu R, Cock C, Rommel N, et al. Inter-rater reliability and validity of automated impedance manometry analysis and fluoroscopy in dysphagic patients after head and neck cancer radiotherapy. Neurogastroenterol Motil. 2015;27(8):1183-9.

573. Omari TI, Savilampi J, Kokkinn K, Schar M, Lamvik K, Doeltgen S, et al. The Reliability of Pharyngeal High Resolution Manometry with Impedance for Derivation of Measures of Swallowing Function in Healthy Volunteers. Int J Otolaryngol. 2016;2016:2718482.

574. Omari TI, Papathanasopoulos A, Dejaeger E, Wauters L, Scarpellini E, Vos R, et al. Reproducibility and agreement of pharyngeal automated impedance manometry with videofluoroscopy. Clin Gastroenterol Hepatol. 2011;9(10):862-7.

575. Silva LC, Herbella FA, Neves LR, Vicentine FP, Neto SP, Patti MG. Anatomophysiology of the pharyngo-upper esophageal area in light of high-resolution manometry. J Gastrointest Surg. 2013;17(12):2033-8.

576. Matsubara K, Kumai Y, Samejima Y, Yumoto E. Propagation Curve and Velocity of Swallowing Pressure in Healthy Young Adults. Dysphagia. 2015;30(6):674-9.

577. Park D, Lee HH, Lee ST, Oh Y, Lee JC, Nam KW, et al. Normal contractile algorithm of swallowing related muscles revealed by needle EMG and its comparison to videofluoroscopic swallowing study and high resolution manometry studies: A preliminary study. Journal of Electromyography and Kinesiology. 2017;36:81-9.

578. Yoon KJ, Park JH, Park JH, Jung IS. Videofluoroscopic and manometric evaluation of

pharyngeal and upper esophageal sphincter function during swallowing. J Neurogastroenterol Motil. 2014;20(3):352-61.

579. Jiao H, Mei L, Sharma T, Kern M, Sanvanson P, Shaker R. A human model of restricted upper esophageal sphincter opening and its pharyngeal and UES deglutitive pressure phenomena. Am J Physiol Gastrointest Liver Physiol. 2016;311(1):G84-90.

580. Hoffman MR, Jones CA, Geng Z, Abelhalim SM, Walczak CC, Mitchell AR, et al. Classification of high-resolution manometry data according to videofluoroscopic parameters using pattern recognition. Otolaryngol Head Neck Surg. 2013;149(1):126-33.

581. Ferris L, Omari T, Selleslagh M, Dejaeger E, Tack J, Vanbeckevoort D, et al. Pressure flow analysis in the assessment of preswallow pharyngeal bolus presence in Dysphagia. Int J Otolaryngol. 2015;2015:764709.

582. O'Rourke A, Humphries K, Lazar A, Martin-Harris B. The pharyngeal contractile integral is a useful indicator of pharyngeal swallowing impairment. Neurogastroenterol Motil. 2017;29(12).

583. Omari TI, Dejaeger E, Tack J, Van Beckevoort D, Rommel N. Effect of Bolus Volume and Viscosity on Pharyngeal Automated Impedance Manometry Variables Derived for Broad Dysphagia Patients. Dysphagia. 2012;28(2):146-52.

584. Park C-H, Kim D-K, Lee Y-T, Yi Y, Lee J-S, Kim K, et al. Quantitative Analysis of Swallowing Function Between Dysphagia Patients and Healthy Subjects Using High-Resolution Manometry. Annals of Rehabilitation Medicine. 2017;41(5).

585. Park D, Oh Y, Ryu JS. Findings of Abnormal Videofluoroscopic Swallowing Study Identified by High-Resolution Manometry Parameters. Arch Phys Med Rehabil. 2016;97(3):421-8.

586. Geng Z, Hoffman MR, Jones CA, McCulloch TM, Jiang JJ. Three-dimensional analysis of pharyngeal high-resolution manometry data. Laryngoscope. 2013;123(7):1746-53.

587. Donabedian A. Evaluating the Quality of Medical Care. The Milbank Quarterly. 2005;83(4):691-729.

588. Jones CA, Meisner EL, Broadfoot CK, Rosen SP, Samuelsen CR, McCulloch TM. Methods for measuring swallowing pressure variability using high-resolution manometry. Front Appl Math Stat. 2018;4.

589. Kern MK, Balasubramanian G, Sanvanson P, Agrawal D, Wuerl A, Shaker R. Pharyngeal peristaltic pressure variability, operational range, and functional reserve. Am J Physiol Gastrointest Liver Physiol. 2017;312(5):G516-G25.

590. Balasubramanian G, Sharma T, Kern M, Mei L, Sanvanson P, Shaker R. Characterization of pharyngeal peristaltic pressure variability during volitional swallowing in healthy individuals. Neurogastroenterol Motil. 2017;29(11).

591. Cock C, Besanko L, Kritas S, Burgstad CM, Thompson A, Heddle R, et al. Maximum upper esophageal sphincter (UES) admittance: a non-specific marker of UES dysfunction. Neurogastroenterol Motil. 2016;28(2):225-33.

592. Cock C, Omari TI, Burgstad CM, Thompson A, Doeltgen SH. Biomechanical correlates of sequential drinking behavior in aging. Neurogastroenterol Motil. 2020:e13945.

593. Cock C, Omari T. Systematic Review of Pharyngeal and Esophageal Manometry in Healthy or Dysphagic Older Persons (>60 years). Geriatrics (Basel). 2018;3(4).

594. Guiu Hernandez E, Gozdzikowska K, Jones RD, Huckabee ML. Pharyngeal Swallowing During Wake and Sleep. Dysphagia. 2019;34(6):916-21.

595. Hoffman MR, Ciucci MR, Mielens JD, Jiang JJ, McCulloch TM. Pharyngeal swallow adaptations to bolus volume measured with high-resolution manometry. Laryngoscope.

2010;120(12):2367-73.

596. Suh JH, Park D, Kim IS, Kim H, Shin CM, Ryu JS. Feasibility of high-resolution manometry for decision of feeding methods in patients with amyotrophic lateral sclerosis. Medicine (Baltimore). 2019;98(23):e15781.

597. Jones CA, Hoffman MR, Lin L, Abdelhalim S, Jiang JJ, McCulloch TM. Identification of swallowing disorders in early and mid-stage Parkinson's disease using pattern recognition of pharyngeal high-resolution manometry data. Neurogastroenterol Motil. 2018;30(4):e13236.

598. Taira K, Fujiwara K, Fukuhara T, Koyama S, Morisaki T, Takeuchi H. Evaluation of the pharynx and upper esophageal sphincter motility using high-resolution pharyngeal manometry for Parkinson's disease. Clin Neurol Neurosurg. 2021;201:106447.

599. Lee T, Park JH, Sohn C, Yoon KJ, Lee YT, Park JH, et al. Failed Deglutitive Upper Esophageal Sphincter Relaxation Is a Risk Factor for Aspiration in Stroke Patients with Oropharyngeal Dysphagia. J Neurogastroenterol Motil. 2017;23(1):34-40.

600. Sung HY, Lee K-S, Choi M-G, Kim J-S. Dysphagia Screening Using High-resolution Impedance Manometry in Acute Stroke. International Journal of Gerontology. 2018;12(2):110-5.

601. Pinna BR, Herbella FAM, de Biase N, Vaiano TCG, Patti MG. High-Resolution Manometry Evaluation of Pressures at the Pharyngo-upper Esophageal Area in Patients with Oropharyngeal Dysphagia Due to Vagal Paralysis. Dysphagia. 2017;32(5):657-62.

602. Lippert D, Hoffman MR, Britt CJ, Jones CA, Hernandez J, Ciucci MR, et al. Preliminary Evaluation of Functional Swallow After Total Laryngectomy Using High-Resolution Manometry. Ann Otol Rhinol Laryngol. 2016;125(7):541-9.

603. Zhang T, Szczesniak M, Maclean J, Bertrand P, Wu PI, Omari T, et al. Biomechanics of Pharyngeal Deglutitive Function following Total Laryngectomy. Otolaryngol Head Neck Surg. 2016;155(2):295-302.

604. Santos TL, Herbella FAM, Azevedo RR. The applicability of high resolution manometry in total laryngectomy. Codas. 2020;32(6):e20190006.

605. Kallusky J, Zimmerer R, Tavassol F, Gellrich NC, Ptok M, Jungheim M. Deglutition in Patients With Hypernasality Associated With Unilateral Cleft Lip and Palate Evaluated With High-Resolution Manometry. Cleft Palate Craniofac J. 2020;57(2):238-44.

606. Lee TH, Lee JS. High-resolution Manometry for Oropharyngeal Dysphagia in a Patient With Large Cervical Osteophytes. J Neurogastroenterol Motil. 2012;18(3):338-9.

607. Kunieda K, Fujishima I, Wakabayashi H, Ohno T, Shigematsu T, Itoda M, et al. Relationship Between Tongue Pressure and Pharyngeal Function Assessed Using High-Resolution Manometry in Older Dysphagia Patients with Sarcopenia: A Pilot Study. Dysphagia. 2020.

608. Hutcheson KA, Hammer MJ, Rosen SP, Jones CA, McCulloch TM. Expiratory muscle strength training evaluated with simultaneous high-resolution manometry and electromyography. Laryngoscope. 2017;127(4):797-804.

609. Doeltgen SH, Rigney L, Cock C, Omari T. Effects of cortical anodal transcranial direct current stimulation on swallowing biomechanics. Neurogastroenterol Motil. 2018;30(11):e13434.

610. Meisoll FJ, Jungheim M, Fast JF, Miller S, Ptok M. Upper Esophageal Sphincter Response to Laryngeal Adductor Reflex Elicitation in Humans. Laryngoscope. 2020.

611. Suntrup-Krueger S, Muhle P, Kampe I, Egidi P, Ruck T, Lenze F, et al. Effect of Capsaicinoids on Neurophysiological, Biochemical, and Mechanical Parameters of Swallowing Function. Neurotherapeutics. 2021.

612. Doeltgen SH, Omari TI, Savilampi J. Remifentanil alters sensory neuromodulation of

swallowing in healthy volunteers: quantification by a novel pressure-impedance analysis. Am J Physiol Gastrointest Liver Physiol. 2016;310(11):G1176-82.

613. Savilampi J, Omari T, Magnuson A, Ahlstrand R. Effects of remifentanil on pharyngeal swallowing: A double blind randomised cross-over study in healthy volunteers. Eur J Anaesthesiol. 2016;33(9):622-30.

614. Doeltgen SH, Ong E, Scholten I, Cock C, Omari T. Biomechanical Quantification of Mendelsohn Maneuver and Effortful Swallowing on Pharyngoesophageal Function. Otolaryngol Head Neck Surg. 2017;157(5):816-23.

615. Winiker K, Gozdzikowska K, Guiu Hernandez E, Kwong SL, Macrae P, Huckabee ML. Potential for Behavioural Pressure Modulation at the Upper Oesophageal Sphincter in Healthy Swallowing. Dysphagia. 2021.

616. Aoyagi Y, Ohashi M, Ando S, Inamoto Y, Aihara K, Matsuura Y, et al. Effect of Tongue-Hold Swallow on Pharyngeal Contractile Properties in Healthy Individuals. Dysphagia. 2021;36(5):936-43.

617. Meyer JP, Jones CA, Walczak CC, McCulloch TM. Three-dimensional manometry of the upper esophageal sphincter in swallowing and nonswallowing tasks. Laryngoscope. 2016;126(11):2539-45.

618. Balou M, McCullough GH, Aduli F, Brown D, Stack BC, Jr., Snoddy P, et al. Manometric measures of head rotation and chin tuck in healthy participants. Dysphagia. 2014;29(1):25-32.

619. Kim CK, Ryu JS, Song SH, Koo JH, Lee KD, Park HS, et al. Effects of Head Rotation and Head Tilt on Pharyngeal Pressure Events Using High Resolution Manometry. Annals of Rehabilitation Medicine. 2015;39(3).

620. Hammer MJ, Jones CA, Mielens JD, Kim CH, McCulloch TM. Evaluating the tongue-hold maneuver using high-resolution manometry and electromyography. Dysphagia. 2014;29(5):564-70.

621. Umeki H, Takasaki K, Enatsu K, Tanaka F, Kumagami H, Takahashi H. Effects of a tongue-holding maneuver during swallowing evaluated by high-resolution manometry. Otolaryngol Head Neck Surg. 2009;141(1):119-22.

622. Rosen SP, Abdelhalim SM, Jones CA, McCulloch TM. Effect of Body Position on Pharyngeal Swallowing Pressures Using High-Resolution Manometry. Dysphagia. 2018;33(3):389-98.

623. Heslin N, Regan J. Effect of effortful swallow on pharyngeal pressures during swallowing in adults with dysphagia: A pharyngeal high-resolution manometry study. Int J Speech Lang Pathol. 2021:1-10.

624. Wu P, Szczesniak M, Omari T, Lam T, Wong M, Maclean J, et al. Cricopharyngeal Peroral Endoscopic Myotomy Improves Ooropharyngeal Dysphagia in Patients with Parkinson's Disease.pdf. Endoscopy International Open - accepted for publication. 2021.

625. Fujiwara K, Koyama S, Taira K, Kawamoto K, Fukuhara T, Takeuchi H. Evaluation of pharyngeal swallowing pressure using high-resolution manometry during transoral surgery for oropharyngeal cancer. J Laryngol Otol. 2021;135(2):153-8.

626. Regan J. Impact of Sensory Stimulation on Pharyngo-esophageal Swallowing Biomechanics in Adults with Dysphagia: A High-Resolution Manometry Study. Dysphagia. 2020;35(5):825-33.

627. Matsubara K, Kumai Y, Miyamoto T, Samejima Y, Yoshida N, Baba H, et al. The effect of a chin-down maneuver after esophagectomy on oropharyngeal swallowing pressure measured using high-resolution manometry. Auris Nasus Larynx. 2020;47(1):141-7.

628. Romain D, Evans LK, Diaz Y, Allen K, Galek K. Biofeedback Training Improves Swallowing

in a Unique Case of Upper Esophageal Sphincter Hypotonicity. Laryngoscope. 2020.

629. Kammer R, Jones C, Johnson A, Dailey S, McCulloch T, Thibeault S. High-resolution manometry and swallow outcomes after vocal fold injection medialization for unilateral vocal fold paralysis/paresis. Head Neck. 2019;41(7):2389-97.

630. Pinna BR, Herbella FAM, de Biase N. Pharyngeal motility in patients submitted to type I thyroplasty. Braz J Otorhinolaryngol. 2021.

631. O'Rourke A, Humphries K. The use of high-resolution pharyngeal manometry as biofeedback in dysphagia therapy. ENT Journal. 2017;96(2):56-8.

632. Juan J, Hind J, Jones C, McCulloch T, Gangnon R, Robbins J. Case study: application of isometric progressive resistance oropharyngeal therapy using the Madison Oral Strengthening Therapeutic device. Top Stroke Rehabil. 2013;20(5):450-70.

633. Lan Y, Xu G, Dou Z, Wan G, Yu F, Lin T. Biomechanical changes in the pharynx and upper esophageal sphincter after modified balloon dilatation in brainstem stroke patients with dysphagia. Neurogastroenterol Motil. 2013;25(12):e821-9.

634. Lee SM, Lee BH, Kim JW, Jang JY, Jang EG, Ryu JS. Effects of Chin-Down Maneuver on Pharyngeal Pressure Generation According to Dysphagia and Viscosity. Ann Rehabil Med. 2020;44(6):493-501.

635. Park CH, Lee YT, Yi Y, Lee JS, Park JH, Yoon KJ. Ability of High-Resolution Manometry to Determine Feeding Method and to Predict Aspiration Pneumonia in Patients With Dysphagia. Am J Gastroenterol. 2017;112(7):1074-83.

636. Pang KP, Vicini C, Montevecchi F, Piccin O, Chandra S, Yang HC, et al. Long-term Complications of Palate Surgery: A Multicenter Study of 217 Patients. Laryngoscope. 2020;130(9):2281-4.

637. Christensen M, Trapl M. Development of a modified swallowing screening tool to manage post-extubation dysphagia. Nurs Crit Care. 2018;23(2):102-7.

638. Smithard DG. Neuromuscular disease and extubation dysphagia. Crit Care. 2013;17(5):194.

639. Hunter KU, Schipper M, Feng FY, Lyden T, Haxer M, Murdoch-Kinch CA, et al. Toxicities affecting quality of life after chemo-IMRT of oropharyngeal cancer: prospective study of patient-reported, observer-rated, and objective outcomes. Int J Radiat Oncol Biol Phys. 2013;85(4):935-40.

640. Kraaijenga SA, Oskam IM, van der Molen L, Hamming-Vrieze O, Hilgers FJ, van den Brekel MW. Evaluation of long term (10-years+) dysphagia and trismus in patients treated with concurrent chemo-radiotherapy for advanced head and neck cancer. Oral Oncol. 2015;51(8):787-94.

641. Crowder SL, Najam N, Sarma KP, Fiese BH, Arthur AE. Head and Neck Cancer Survivors' Experiences with Chronic Nutrition Impact Symptom Burden after Radiation: A Qualitative Study. J Acad Nutr Diet. 2020;120(10):1643-53.

642. Fraser A, Odelli C, Britton B, Kumar M, Day F, Tieu MT, et al. Gastrostomy dependency trends over 15 years of patients at a large tertiary referral center following the insertion of a prophylactic gastrostomy for chemoradiation for mucosal head and neck cancer. Asia Pac J Clin Oncol. 2020;16(5):e198-e206.

643. Axelsson L, Silander E, Nyman J, Bove M, Johansson L, Hammerlid E. Effect of prophylactic percutaneous endoscopic gastrostomy tube on swallowing in advanced head and neck cancer: A randomized controlled study. Head Neck. 2017;39(5):908-15.

644. Govender R, Smith CH, Barratt H, Gardner B, Taylor SA. SIP SMART: a parallel group randomised feasibility trial of a tailored pre-treatment swallowing intervention package compared with usual care for patients with head and neck cancer. BMC Cancer. 2020;20(1):360.

645. Perry A, Lee SH, Cotton S, Kennedy C. Therapeutic exercises for affecting post-treatment swallowing in people treated for advanced-stage head and neck cancers. Cochrane Database Syst Rev. 2016(8):CD011112.

646. Hinther A, Samson N, Lau H, Quon H, Banerjee R, Lysack JT, et al. Volumetric changes in pharyngeal structures following head and neck cancer chemoradiation therapy. Laryngoscope. 2020;130(3):597-602.

647. Garber D, Rotsides J, Abu-Ghanem S, Bandler I, Smith A, O'yfe I, et al. Decreased tongue volume post radiation Annals of Otology, Rhinology & Laryngology. 2020:1-7.

648. Phulpin B, Gangloff P, Tran N, Bravetti P, Merlin JL, Dolivet G. Rehabilitation of irradiated head and neck tissues by autologous fat transplantation. Plast Reconstr Surg. 2009;123(4):1187-97.

649. Kraaijenga SA, Lapid O, van der Molen L, Hilgers FJ, Smeele LE, van den Brekel MW. Feasibility and potential value of lipofilling in post-treatment oropharyngeal dysfunction. Laryngoscope. 2016;126(12):2672-8.

650. Szczesniak M, Maclean J, Zhang T, Liu R, Cook I. The normative range for and age and gender effects on the Sydney Swallow Questionnaire (SSQ). Dysphagia. 2014;29(5):535-8.

651. Wallace KL, Middleton S, Cook IJ. Development and Validation of a Self-report Symptom Inventory to Assess the Severity of Oral-Pharyngeal Dysphagia. Gastroenterology. 2000;118:678-87.

652. Crary MA, Mann GD, Groher ME. Initial psychometric assessment of a functional oral intake scale for dysphagia in stroke patients. Arch Phys Med Rehabil. 2005;86(8):1516-20.

653. Colodny N. Interjudge and Intrajudge Reliabilities in Fiberoptic Endoscopic Evaluation of Swallowing (Fees®) Using the Penetration–Aspiration Scale: A Replication Study. Dysphagia. 2002;17:308-15.

654. Daggett A, Logemann J, Rademaker A, Pauloski B. Laryngeal penetration during deglutition in normal subjects of various ages. Dysphagia. 2006;21(4):270-4.

655. Steele CM, Namasivayam-MacDonald AM, Guida BT, Cichero JA, Duivestein J, Hanson B, et al. Creation and Initial Validation of the International Dysphagia Diet Standardisation Initiative Functional Diet Scale. Arch Phys Med Rehabil. 2018;99(5):934-44.

656. https://creativecommons.org/licenses/by-sa/4.0/legalcode. LutCASL. The International Dysphagia Diet Standardised Initiative 2019. 2019.

657. Meyers C, Milici J, Robison R. The ability of two chlorine dioxide chemistries to inactivate human papillomavirus-contaminated endocavitary ultrasound probes and nasendoscopes. J Med Virol. 2020;92(8):1298-302.

658. Heinzer R, Vat S, Marques-Vidal P, Marti-Soler H, Andries D, Tobback N, et al. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. The Lancet Respiratory Medicine. 2015;3(4):310-8.

659. Johns M, W. A new method for measuring daytime sleepiness: The Epwoth Sleepiness Scale. Sleep. 1991;14(6):540-5.

660. Pizzorni N, Radovanovic D, Pecis M, Lorusso R, Annoni F, Bartorelli A, et al. Dysphagia symptoms in obstructive sleep apnea: prevalence and clinical correlates. Respir Res. 2021;22(1):117.

661. Kato T, Abe K, Mikami A, Sugita H, Muraki H, Okura M, et al. Subjective oropharyngeal symptoms for abnormal swallowing in Japanese patients with obstructive sleep apnea syndrome: a descriptive questionnaire study. Cranio. 2016;34(2):95-9.

662. Caparroz FA, de Almeida Torres Campanholo M, Sguillar DA, Haddad L, Park SW, Bittencourt L, et al. A pilot study on the efficacy of continuous positive airway pressure on the manifestations of dysphagia in patients with obstructive sleep apnea. Dysphagia. 2019;34(3):333-40.

663. Jardine M, Miles A, Allen JE. Swallowing function in advanced age. Curr Opin Otolaryngol Head Neck Surg. 2018;26(6):367-74.

664. Valarelli LP, Corradi AMB, Grechi TH, Eckeli AL, Aragon DC, Kupper DS, et al. Cephalometric, muscular and swallowing changes in patients with OSAS. J Oral Rehabil. 2018;45(9):692-701.

665. Cook I, Gabb M, Panagoploulos V, Jamieson G, Dodds W, Dent J, et al. Pharyngeal (Zenker's) Diverticulum Is a Disorder of Upper Esophageal Sphincter Opening. Gastroenterology. 1992;103:1229-35.

666. Dantas R, Cook I, Dodds W, Kern M, Lang I, Brasseur J. Biomechanics of Cricopharyngeal Bars. Gastroenterology. 1990;99:1269-74.

667. Kendall KA, Leonard R, McKenzie S. Accommodation to changes in bolus viscosity in normal deglutition: A videofluorscopic study. Ann Otol Rhinol Laryngol. 2001;110:1059-65.

668. Genta PR, Schorr F, Eckert DJ, Gebrim E, Kayamori F, Moriya HT, et al. Upper airway collapsibility is associated with obesity and hyoid position. Sleep. 2014;37(10):1673-8.

669. Nguyen AJ, V., Payne R, Beauregard JN, N. , Kimoff R. Laryngeal and velopharyngeal sensory impairment in obstructive sleep apnea. Sleep. 2005;28(5):585-93.

670. Saboisky JP, Stashuk DW, Hamilton-Wright A, Carusona AL, Campana LM, Trinder J, et al. Neurogenic changes in the upper airway of patients with obstructive sleep apnea. Am J Respir Crit Care Med. 2012;185(3):322-9.

671. Vroegop AV, Vanderveken OM, Boudewyns AN, Scholman J, Saldien V, Wouters K, et al. Drug-induced sleep endoscopy in sleep-disordered breathing: report on 1,249 cases. Laryngoscope. 2014;124(3):797-802.

672. Perry JL. Anatomy and physiology of the velopharyngeal mechanism. Semin Speech Lang. 2011;32(2):83-92.

673. Matsubara K, Kumai Y, Kamenosono Y, Samejima Y, Yumoto E. Effect of three different chin-down maneuvers on swallowing pressure in healthy young adults. Laryngoscope. 2016;126(2):437-41.

674. Parreira LC, Salgado-Junior W, Dantas RO. Swallowing in Obese Individuals before and after Bariatric Surgery. Obes Surg. 2020;30(9):3522-7.

675. da Paz Oliveira LA, Fontes LH, Cahali MB. Swallowing and pharyngo-esophageal manometry in obstructive sleep apnea. Braz J Otorhinolaryngol. 2015;81(3):294-300.

676. Dodds WJ, Logeann J, Stewart E. Radiologic Assessment of Abnormal Oral and Pharyngeal Phases of Swallowing. American Journal of Reoentgenology. 1990;154:965-74.

677. Singendonk M, Kritas S, Omari T, Feinle-Bisset C, Page AJ, Frisby CL, et al. Upper Gastrointestinal Function in Morbidly Obese Adolescents Before and 6 Months After Gastric Banding. Obes Surg. 2018;28(5):1277-88.

678. Chiffer RC, Schwab RJ, Keenan BT, Borek RC, Thaler ER. Volumetric MRI analysis pre- and post-Transoral robotic surgery for obstructive sleep apnea. Laryngoscope. 2015;125(8):1988-95.

679. Sutherland K, Lowth A, Antic N, Carney S, Catcheside P, Chai-Coetzer C-L, et al. Volumetric MRI analysis of Multilevel Upper Airway Surgery effects on pharyngeal structure. 2021.

680. Stuck BA, Kopke J, Hormann K, Verse T, Eckert A, Bran G, et al. Volumetric tissue reduction in radiofrequency surgery of the tongue base. Otolaryngol Head Neck Surg. 2005;132(1):132-5.

681. Butler SG, Maslan J, Stuart A, Leng X, Wilhelm E, Lintzenich CR, et al. Factors influencing bolus dwell times in healthy older adults assessed endoscopically. Laryngoscope. 2011;121(12):2526-34.

682. Schar M, Omari T, Woods C, Ferris L, Doeltgen S, Kushington K, et al. Altered swallowing biomechanics in people with moderate-severe obstructive sleep apnea. Journal of Clinical Sleep Medicine. 2021;in press.

683. Powell NB, Riley RW, Guilleminault C. Radiofrequency tongue base reduction in sleep-disordered breathing: A pilot study. Otolaryngol Head Neck Surg. 1999;120(5):656-64.

684. Detsky ME, Harhay MO, Bayard DF, Delman AM, Buehler AE, Kent SA, et al. Six-Month Morbidity and Mortality among Intensive Care Unit Patients Receiving Life-Sustaining Therapy. A Prospective Cohort Study. Ann Am Thorac Soc. 2017;14(10):1562-70.

685. Ferrante LE, Pisani MA, Murphy TE, Gahbauer EA, Leo-Summers LS, Gill TM. Factors Associated with Functional Recovery among Older Intensive Care Unit Survivors. Am J Respir Crit Care Med. 2016;194(3):299-307.

686. See KC, Peng SY, Phua J, Sum CL, Concepcion J. Nurse-performed screening for postextubation dysphagia: a retrospective cohort study in critically ill medical patients. Critical Care. 2016;20:326-34.

687. Johnson KL, Speirs L, Mitchell A, Przybyl H, Anderson D, Manos B, et al. Validation of a Postextubation Dysphagia Screening Tool for Patients After Prolonged Endotracheal Intubation. Am J Crit Care. 2018;27(2):89-96.

688. Marian T, Dünser M, Citerio G, Koköfer A, Dziewas R. Are intensive care physicians aware of dysphagia? The MADICU survey results. Intensive Care Medicine. 2018.

689. van Snippenburg W, Kroner A, Flim M, Hofhuis J, Buise M, Hemler R, et al. Awareness and Management of Dysphagia in Dutch Intensive Care Units: A Nationwide Survey. Dysphagia. 2019;34(2):220-8.

690. Perren A, Zurcher P, Schefold JC. Clinical Approaches to Assess Post-extubation Dysphagia (PED) in the Critically Ill. Dysphagia. 2019;34(4):475-86.

691. Brodsky MB, Pandian V, Needham DM. Post-extubation dysphagia: a problem needing multidisciplinary efforts. Intensive Care Med. 2020;46(1):93-6.

692. Duncan S. Swallowing intervention outcomes in critical care: development of a core outcone set. Professionals, Version 2.0. In: Schar M, editor. Belfast, Ireland: Queen's University Belfast; 2021.

693. Leder SB, Warner HL, Suiter DM, Young NO, Bhattacharya B, Siner JM, et al. Evaluation of Swallow Function Post-Extubation: Is It Necessary to Wait 24 Hours? Annals of Otology, Rhinology & Laryngology. 2019;128(7):619-24.

694. Thille AW, Harrois A, Schortgen F, Brun-Buisson C, Brochard L. Outcomes of extubation failure in medical intensive care unit patients. Crit Care Med. 2011;39(12):2612-8.

695. Topal AE, Eren MN. Risk factors for the development of pneumonia post cardiac surgery. Cardiovasc J Afr. 2012;23(4):212-5.

696. Adly A, Youssef TA, El-Begermy MM, Younis HM. Timing of tracheostomy in patients with prolonged endotracheal intubation: a systematic review. Eur Arch Otorhinolaryngol. 2018;275(3):679-90.

697. Knaus WA, Wagner DP, Draper EA, Zimmerman JE, Bergner M, Bastos PG, et al. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. Chest. 1991;100(6):1619-36.

698. Charlson M, Pompei P, Ales K, MacKenzie C. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. Journal of Chronic Diseases. 1987;40:373-83.

699. Ware J, Sherbourne C. The MOS 36-item short-form health survey (SF-36).I. Conceptual framework and item selection. Medical Care. 1992.

700. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ. 2005;173(5):489-95.

701. Skoretz SA, Riopelle SJ, Wellman L, Dawson C. Investigating Swallowing and Tracheostomy Following Critical Illness: A Scoping Review. Crit Care Med. 2020;48(2):e141-e51.

702. Tanaka A, Isono S, Ishikawa T, Nishino T. Laryngeal Reflex before and after Placement of Airway Interventions: Endotracheal Tube and Laryngeal Mask Airway. Anesthesiology. 2005;102(1):20-5.

703. Muramatsu K, Matsuo K, Kawai Y, Yamamoto T, Hara Y, Shimomura Y, et al. Comparison of wiping and rinsing techniques after oral care procedures in critically ill patients during endotracheal intubation and after extubation: A prospective cross-over trial. Jpn J Nurs Sci. 2019;16(1):80-7.

704. de Lima Alvarenga EH, Dall'Oglio GP, Murano EZ, Abrahao M. Continuum theory: presbyphagia to dysphagia? Functional assessment of swallowing in the elderly. Eur Arch Otorhinolaryngol. 2018;275(2):443-9.

705. Jardine M, Miles A, Allen J. Dysphagia Onset in Older Adults during Unrelated Hospital Admission: Quantitative Videofluoroscopic Measures. Geriatrics (Basel). 2018;3(4).

706. Wirth R, Dziewas, R, Beck, A.M., Clavé, P, Hamdy, S, Heppner, H.J, Langmore, S, Leischker, A.H, Martino, R, Pluschinski, P, Rösler, A, Shaker, R, Warnecke, T, Sieber, C.C, Volkert, D. Oropharyngeal dysphagia in older persons - from pathophysiology to adequate intervention: a review and summary of an international expert meeting. Clinical Intervention in Aging. 2016;11:189-208.

707. Correia M, Waitzberg D. The impact of malnutrition on morbidity, mortality, length of hospital stay and costs evaluated through a multivariate model analysis. Clinical Nutrition. 2003;22(3):235-9.

708. Ridley EJ, Parke RL, Davies AR, Bailey M, Hodgson C, Deane AM, et al. What Happens to Nutrition Intake in the Post-Intensive Care Unit Hospitalization Period? An Observational Cohort Study in Critically Ill Adults. JPEN J Parenter Enteral Nutr. 2019;43(1):88-95.

709. Furkim AM, da Silva RG, Vanin G, Martino R. The association between temporal measures of swallowing with penetration and aspiration in patients with dysphagia: A meta-analysis. NeuroRehabilitation. 2019;44(1):111-29.

710. Shaker R, Ren, J., Zamir, Z, Sarna, A, Liu, J & Sui, Z. Effect of Aging, position and temperature on the threhold volume triggering pharyngeal swallows. Gastroenterology. 1994;107:396-402.

711. Cedborg A, Sundman E, Bodén K, Hedström H, Kuylenstierna R, Ekberg O, et al. Effects of Morphine and Midazolam on Pharyngeal Function, Airway Protection, and Coordination of Breathing and Swallowing in Healthy Adults. Anesthesiology. 2015;122:1253-67.

712. Shaker R, Ren J, Xie P, Lang I, Bardan E, Sui Z. Characterization of the pharyngo-UES contractile reflex in humans. Gastrointest Liver Physiol. 1997;36:G854-G8.

713. Schefold JC, Bierbrauer J, Weber-Carstens S. Intensive care unit-acquired weakness (ICUAW) and muscle wasting in critically ill patients with severe sepsis and septic shock. J Cachexia Sarcopenia Muscle. 2010;1(2):147-57.

714. Lacomis D. Neuromuscular Disorders in Critically Ill Patients: Review and Update. Journal of Clinical Neuromuscular Disease. 2011;12(4):197-218.

715. Wakabayashi H, Takahashi R, Watanabe N, Oritsu H, Shimizu Y. Prevalence of skeletal muscle mass loss and its association with swallowing function after cardiovascular surgery. Nutrition. 2017;38:70-3.

716. Su H, Hsiao TY, Ku SC, Wang TG, Lee JJ, Tzeng WC, et al. Tongue weakness and somatosensory disturbance following oral endotracheal extubation. Dysphagia. 2015;30(2):188-95.

717. Aoyagi Y, Ohashi M, Funahashi R, Otaka Y, Saitoh E. Oropharyngeal Dysphagia and Aspiration Pneumonia Following Coronavirus Disease 2019: A Case Report. Dysphagia. 2020;35(4):545-8.

718. Messing B, Ward E, Lazarus C, Ryniak K, Kim M, Silinonte J, et al. Establishing a Multidisciplinary Head and Neck Clinical Pathway: An Implementation Evaluation and Audit of Dysphagia-Related Services and Outcomes. 2018.

719. Baijens L, Walshe M, Aaltonen L, Arens C, Cordier R, Cras P, et al. European white paper: oropharyngeal dysphagia in head and neck cancer. Eur Arch Otorhinolaryngol. 2020.

720. Ishii R, Kato K, Ohkoshi A, Sato T, Hirano A, Ogawa T, et al. Simultaneous evaluation of symptoms, swallowing functions, and patient-reported swallowing difficulties and their correlations with ingestion status during definitive chemoradiotherapy for oropharyngeal and hypopharyngeal cancer. Support Care Cancer. 2021;29(2):955-64.

721. Arrese LC, Schieve HJ, Graham JM, Stephens JA, Carrau RL, Plowman EK. Relationship between oral intake, patient perceived swallowing impairment, and objective videofluoroscopic measures of swallowing in patients with head and neck cancer. Head & Neck. 2018;41(4):1016-23.

722. Omari TI, Ferris L, Schar M, Cock C, Doeltgen S. Multiple swallow behaviour during high resolution pharyngeal manometry: prevalence and sub-typing in healthy adults. Speech, Language and Hearing. 2020:1-7.

723. Dworkin JP, Hill SL, Stachler RJ, Meleca RJ, Kewson D. Swallowing function outcomes following nonsurgical therapy for advanced-stage laryngeal carcinoma. Dysphagia. 2006;21(1):66-74.

724. Chang YC, Chen SY, Lui LT, Wang TG, Wang TC, Hsiao TY, et al. Dysphagia in patients with nasopharyngeal cancer after radiation therapy: a videofluoroscopic swallowing study. Dysphagia. 2003;18(2):135-43.

725. Bleier B, Levine M, Mick R, Rubesin S, Sack M, SZ. , McKinney K, et al. Dysphagia After Chemoradiation: Analysis by Modified Barium Swallow. Annals of Otology, Rhinology & Laryngology. 2007;116(1):837-41.

726. Pauloski BR, Logemann JA, Rademaker AW, Lundy D, Sullivan PA, Newman LA, et al. Effects of enhanced bolus flavors on oropharyngeal swallow in patients treated for head and neck cancer. Head Neck. 2013;35(8):1124-31.

727. Choi KH, Ryu JS, Kim MY, Kang JY, Yoo SD. Kinematic analysis of dysphagia: significant parameters of aspiration related to bolus viscosity. Dysphagia. 2011;26(4):392-8.

728. Molfenter SM, Steele CM. Kinematic and temporal factors associated with penetration-aspiration in swallowing liquids. Dysphagia. 2014;29(2):269-76.

729. Roldan C, Johnson C, Lee S-O, Peng A, Dougherty P, Huh B. Subclinical periphral neuropathy in patients with Head and Neck Cancer: A quantitative sensory testing (QST) study.

Pain Physician. 2018;21:E419-E27.

730. Kendall K, S. M, R. L, . Dynamic swallowing study: Objective measures and normative data in adults. In: R L, K K, editors. Dysphagia Assessment and Treatment Planning: A Team Approach 2nd ed. San Diego, CA: Plural Publishing; 2008.

731. Kleinjan KJ, Logemann JA. Effects of repeated wet and dry swallows in healthy adult females. Dysphagia. 2002;17(1):50-6.

732. Robbins J, Coyle J, Rosenbek J, Roecker E, Wood J. Differentiation of Normal and Abnormal Airway Protection during Swallowing Using the Penetration–Aspiration Scale. Dysphagia. 1999;14:228-32.

733. Shapira-Galitz Y, Shoffel-Havakuk H, Halperin D, Lahav Y. Correlation Between Pharyngeal Residue and Aspiration in Fiber-Optic Endoscopic Evaluation of Swallowing: An Observational Study. Arch Phys Med Rehabil. 2019;100(3):488-94.

734. Steele CM, Peladeau-Pigeon M, Barrett E, Wolkin TS. The Risk of Penetration-Aspiration Related to Residue in the Pharynx. Am J Speech Lang Pathol. 2020;29(3):1608-17.

735. Pauloski B, Logemann JA. IMPACT OF TONGUE BASE AND POSTERIOR PHARYNGEAL WALL BIOMECHANICS ON PHARYNGEAL CLEARANCE IN IRRADIATED POSTSURGICAL ORAL AND OROPHARYNGEAL CANCER PATIENTS. Head & Neck. 2000:120-31.

736. Stokely SL, Peladeau-Pigeon M, Leigh C, Molfenter SM, Steele CM. The Relationship Between Pharyngeal Constriction and Post-swallow Residue. Dysphagia. 2015;30(3):349-56.

737. Pal A, Williams R, Cook I, Brassuer J. Intrabolus pressure gradient identifies pathological constriction in the upper esophageal sphincter during flow. Am J Physiol Gastrointest Liver Physiol. 2003;285(5):G1037-G48.

738. Allen JE. Cricopharyngeal function or dysfunction: what's the deal? Curr Opin Otolaryngol Head Neck Surg. 2016;24(6):494-9.

739. Wu PI, Szczesniak MM, Maclean J, Graham PH, Quon H, Choo L, et al. Endoscopic dilatation improves long-term dysphagia following head and neck cancer therapies: a randomized control trial. Dis Esophagus. 2019;32(6).

740. Pauloski B, Rademaker A, Logemann J, Colangelo L. Speech and swallowing in irradiated and noneirradiated postsurgical oral cancer patients. Otolaryngol Head Neck Surg. 1998;118(5):616-24.

741. Szczesniak MM, Maclean J, O'Hare J, Humbert I, Wu PI, Quon H, et al. Videofluoroscopic Swallow Examination Does Not Accurately Detect Cricopharyngeal Radiation Strictures. Otolaryngol Head Neck Surg. 2016;155(3):462-5.

742. Omari TI, Dejaeger E, Tack J, Vanbeckevoort D, Rommel N. An impedance-manometry based method for non-radiological detection of pharyngeal postswallow residue. Neurogastroenterol Motil. 2012;24(7):e277-84.

743. Marur S, Forastiere AA. Head and Neck Squamous Cell Carcinoma: Update on Epidemiology, Diagnosis, and Treatment. Mayo Clin Proc. 2016;91(3):386-96.

744. Watters AL, Cope S, Keller MN, Padilla M, Enciso R. Prevalence of trismus in patients with head and neck cancer: A systematic review with meta-analysis. Head Neck. 2019;41(9):3408-21.

745. Harris A, Lyu L, Wasserman-Winko T, George S, Johnson JT, Nilsen ML. Neck Disability and Swallowing Function in Posttreatment Head and Neck Cancer Patients. Otolaryngol Head Neck Surg. 2020;163(4):763-70.

746. Farwell DG, Rees CJ, Mouadeb DA, Allen J, Chen AM, Enepekides DJ, et al. Esophageal pathology in patients after treatment for head and neck cancer. Otolaryngol Head Neck Surg.

2010;143(3):375-8.

747. Santoso AMM, Jansen F, de Vries R, Leemans CR, van Straten A, Verdonck-de Leeuw IM. Prevalence of sleep disturbances among head and neck cancer patients: A systematic review and meta-analysis. Sleep Med Rev. 2019;47:62-73.

748. Saesen K, van der Veen J, Buyse B, Nuyts S. Obstructive sleep apnea in head and neck cancer survivors. Support Care Cancer. 2021;29(1):279-87.

749. Silva P, Ramos G, Petterle R, Borba V. Sarcopenia as an early complication of patients with head and neck cancer with dysphagia. Eur J Cancer Care (Engl). 2021;30(1):e13343.

750. Leonard R, Rees CJ, Belafsky P, Allen J. Fluoroscopic surrogate for pharyngeal strength: the pharyngeal constriction ratio (PCR). Dysphagia. 2011;26(1):13-7.

751. Messing BP, Ward EC, Lazarus CL, Kim M, Zhou X, Silinonte J, et al. Prophylactic Swallow Therapy for Patients with Head and Neck Cancer Undergoing Chemoradiotherapy: A Randomized Trial. Dysphagia. 2017;32(4):487-500.

752. Mehanna H, Morton R. Deterioration in quality-of-life of late (10-year) survivors of head and neck cancer. Clin Otolaryngol. 2006;31:204-11.

753. Verdonck-de Leeuw IM, Buffart LM, Heymans MW, Rietveld DH, Doornaert P, de Bree R, et al. The course of health-related quality of life in head and neck cancer patients treated with chemoradiation: a prospective cohort study. Radiother Oncol. 2014;110(3):422-8.

754. Pulte D, Brenner H. Changes in survival in head and neck cancers in the late 20th and early 21st century: a period analysis. Oncologist. 2010;15(9):994-1001.

755. Verdonck-de Leeuw IM, van Bleek WJ, Leemans CR, de Bree R. Employment and return to work in head and neck cancer survivors. Oral Oncol. 2010;46(1):56-60.

756. Check DK, Hutcheson KA, Poisson LM, Pocobelli G, Sakoda LC, Zaveri J, et al. Factors associated with employment discontinuation among older and working age survivors of oropharyngeal cancer. Head Neck. 2019;41(11):3948-59.

757. Crowder SL, Douglas KG, Yanina Pepino M, Sarma KP, Arthur AE. Nutrition impact symptoms and associated outcomes in post-chemoradiotherapy head and neck cancer survivors: a systematic review. J Cancer Surviv. 2018;12(4):479-94.

758. Sandmael JA, Sand K, Bye A, Solheim TS, Oldervoll L, Helvik AS. Nutritional experiences in head and neck cancer patients. Eur J Cancer Care (Engl). 2019;28(6):e13168.

759. Terrell J, Ronis D, Fowler K, Bradford C, Chepeha D, Prince M, et al. Clinical Predictors of Quality of Life in Patients With Head and Neck Cancer. Archives of Otolaryngology Head and Neck Surgery. 2004;130(4):401-8.

760. Gurney TA, Eisele DW, Orloff LA, Wang SJ. Predictors of quality of life after treatment for oral cavity and oropharyngeal carcinoma. Otolaryngol Head Neck Surg. 2008;139(2):262-7.

761. Navach V, Calabrese LS, Zurlo V, Alterio D, Funicelli L, Giugliano G. Functional base of tongue fat injection in a patient with severe postradiation Dysphagia. Dysphagia. 2011;26(2):196-9.

762. Ottaviani F, Schindler A, Klinger F, Scarponi L, Succo G, Mozzanica F. Functional fat injection under local anesthesia to treat severe postsurgical dysphagia, case report. Head Neck. 2019;41(1):E17-E21.

763. Hammond SE, Samuels S, Thaller S. Filling in the Details: A Review of Lipofilling of Radiated Tissues in the Head and Neck. J Craniofac Surg. 2019;30(3):667-71.

764. Bukhari SNA, Roswandi NL, Waqas M, Habib H, Hussain F, Khan S, et al. Hyaluronic acid, a promising skin rejuvenating biomedicine: A review of recent updates and pre-clinical and clinical investigations on cosmetic and nutricosmetic effects. Int J Biol Macromol. 2018;120(Pt B):1682-95.

765. Knuf KM, Maani CV, Cummings AK. Clinical agreement in the American Society of Anesthesiologists physical status classification. Perioper Med (Lond). 2018;7:14.

766. Hallen L, Johansson C, Laurent C. Cross-linked hyaluronan (Hylan B gel): a new injectable remedy for treatment of vocal fold insufficiency--an animal study. Acta Otolaryngol. 1999;119(1):107-11.

767. Zeitels S, Lombardo P, Chaves J, Faquin W, Hillman R, Heaton J, et al. Vocal Fold Injection of Absorbable Materials: A Histologic Analysis With Clinical Ramifications. Annals of Otology, Rhinology & Laryngology. 2019;128(35):71S-81S.

768. Tshering Vogel DW, Thoeny HC. Cross-sectional imaging in cancers of the head and neck: how we review and report. Cancer Imaging. 2016;16(1):20.

769. Fong R, Rumbach AF, Ward EC, Doeltgen SH, Sun N, Tsang R. Videofluoroscopic and manometric outcomes of cricopharyngeus balloon dilation for treatment of pharyngo-esophageal dysphagia associated with nasopharyngeal cancer: A case series. Laryngoscope Investigative Otolaryngology. 2021.

770. Baudelet M, Van den Steen L, Duprez F, De Bodt M, Deschuymer S, Goeleven A, et al. Study protocol for a randomized controlled trial: prophylactic swallowing exercises in head-and-neck cancer patients treated with (chemo)radiotherapy (PRESTO trial). Trials. 2020;21(1):237.

771. Jones CA, Rogus-Pulia NM, Forgues AL, Orne J, Macdonald CL, Connor NP, et al. SLP-Perceived Technical and Patient-Centered Factors Associated with Pharyngeal High-Resolution Manometry. Dysphagia. 2019;34(2):170-8.

772. Rogus-Pulia NM, Jones CA, Forgues AL, Orne J, Macdonald CL, Connor NP, et al. Perceived Professional and Institutional Factors Influencing Clinical Adoption of Pharyngeal High-Resolution Manometry. Am J Speech Lang Pathol. 2020;29(3):1550-62.

773. Starmer HM, Quon H, Kumar R, Alcorn S, Murano E, Jones B, et al. The Effect of Radiation Dose on Swallowing: Evaluation of Aspiration and Kinematics. Dysphagia. 2015;30(4):430-7.

774. Bammer T, Salassa JR, Klingler PJ. Comparison of methods for determining cricopharyngeal intrabolus pressure in normal patients as possible indicator for cricopharyngeal myotomy. Otolaryngol Head Neck Surg. 2002;127(4):299-308.

775. Ahuja NK, Chan WW. Assessing Upper Esophageal Sphincter Function in Clinical Practice: a Primer. Curr Gastroenterol Rep. 2016;18(2):7.

776. Regan J, Walshe M, McMahon BP. Current evaluation of upper oesophageal sphincter opening in dysphagia practice: an international SLT survey. Int J Lang Commun Disord. 2012;47(2):156-65.

777. Jones CA, Knigge MA, McCulloch TM. Speech pathologist practice patterns for evaluation and management of suspected cricopharyngeal dysfunction. Dysphagia. 2014;29(3):332-9.

778. Steele CM, Cichero JA. Physiological factors related to aspiration risk: a systematic review. Dysphagia. 2014;29(3):295-304.

779. Cajander P, Omari T, Cock C, Magnuson A, Scheinin M, Savilampi J. Effects of remifentanil on pharyngeal swallowing and esophageal motility - no impact of different bolus volumes, and partial antagonsim by methylnaltrexone. American Journal of Physiology - Gastrointestinal & Liver Physiology. 2021;In-Press.

780. Jehangir A, Tanner S, Malik Z, Parkman HP. Characterizing the proximal esophageal segment in patients with symptoms of esophageal dysmotility. Neurogastroenterol Motil. 2020;32(9):e13888.

781. Yadlapati R, Kahrilas PJ, Fox MR, Bredenoord AJ, Prakash Gyawali C, Roman S, et al. Esophageal motility disorders on high-resolution manometry: Chicago classification version

4.0((c)). Neurogastroenterol Motil. 2021;33(1):e14058.

782. Yip H, Leonard R, Belafsky PC. Can a fluoroscopic estimation of pharyngeal constriction predict aspiration? Otolaryngol Head Neck Surg. 2006;135(2):215-7.

783. Leonard R. Predicting aspiration risk in patients with dysphagia: Evidence from fluoroscopy. Laryngoscope Investig Otolaryngol. 2019;4(1):83-8.

784. Kendall KA, Ellerston J, Heller A, Houtz DR, Zhang C, Presson AP. Objective Measures of Swallowing Function Applied to the Dysphagia Population: A One Year Experience. Dysphagia. 2016;31(4):538-46.

785. Fuller SC, Leonard R, Aminpour S, Belafsky PC. Validation of the pharyngeal squeeze maneuver. Otolaryngol Head Neck Surg. 2009;140(3):391-4.

786. Starmer HM, Dewan K, Kamal A, Khan A, Maclean J, Randall DR. Building an integrated multidisciplinary swallowing disorder clinic: considerations, challenges, and opportunities. Ann N Y Acad Sci. 2020;1481(1):11-9.

787. Wallace ES, Bhutada MA, Broughton WA, Eckert DJ, Garand K. Knowledge, attitudes, and practice patterns of obstructive sleep apnea among speech-language pathologists. Sleep Breath. 2021.

788. Sutherland K, Lowth A, Antic N, Carney A, Catcheside P, Chai-Coetzer C, et al. Volumetric MRI analysis of multilevel upper airway surgery effects of pharyngeal structure. Sleep. 2021-inpress;in-press.

789. Everton LF, Benfield JK, Hedstrom A, Wilkinson G, Michou E, England TJ, et al. Psychometric assessment and validation of the dysphagia severity rating scale in stroke patients. Sci Rep. 2020;10(1):7268.

790. Doeltgen SH, Kaur H, Daniels SK, Mohammadi L, Murray J. Behavioral Interventions Targeting Insufficient Upper Esophageal Sphincter Opening During Swallowing: A Scoping Review. Dysphagia. 2021.

791. Ltd SPAP. Flexible Endoscopic Evaluation of Swallowing (FEES) Clinical Guideline. 2019.

792. Omari T. Swallow GatewayTM for High Resolution Pharyngeal and Esophageal Manometry. 2020.

793. Cichero J, Altman K. Definition, Prevalence and Burden of Oropharyngeal Dysphagia: A Serious Problem among Older Adults Worldwide and the Impact on Prognosis and Hospital Resources. Nestlé Nutr Inst Workshop Ser,. 2012;72:1-11.

794. Dixit S, Sambasivan M. A review of the Australian healthcare system: A policy perspective. SAGE Open Medicine. 2018;6:1-14.

795. Chapel JM, Wang G. Understanding cost data collection tools to improve economic evaluations of health interventions. Stroke Vasc Neurol. 2019;4(4):214-22.

796. Sanders GD, Neumann PJ, Basu A, Brock DW, Feeny D, Krahn M, et al. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. JAMA. 2016;316(10):1093-103.

797. Ravich W, Donner M, Haskins K, Buchholz D, Marsh B, Hendrix T, et al. The swallowing centre: Concepts and procedures. Gastrointestinal Radiology. 1985;10(3):255-61.

798. Litts JK, Abaza MM. Does a multidisciplinary approach to voice and swallowing disorders improve therapy adherence and outcomes? Laryngoscope. 2017;127(11):2446.

799. Welfare AIoHa. Health expenditure Australia 2017–18. Health and welfare expenditure series no.65. Cat. no. HWE 77. Canberra: AIHW.; 2019.

800. Schar MS, Omari TI, Woods CM, Ferris LF, Doeltgen SH, Lushington K, et al. Altered swallowing biomechanics in people with moderate-severe obstructive sleep apnea. J Clin Sleep Med. 2021.

801. Mehdizadeh OB, Dhar SI, Evangelista L, Nativ-Zeltzer N, Bewley AF, Belafsky PC. Prevalence of profound laryngeal sensory neuropathy in head and neck cancer survivors with feeding tube-dependent oropharyngeal dysphagia. Head Neck. 2020;42(5):898-904.

802. Langerman A, MacCracken EK, K. , Haraf D, Vokes E, Stenson K. Aspiration in Chemoradiated Patients With Head and Neck Cancer. Arch Otolaryng Head Neck Surg. 2007;133(12):1289-95.

803. Feng FY, Kim HM, Lyden TH, Haxer MJ, Worden FP, Feng M, et al. Intensity-modulated chemoradiotherapy aiming to reduce dysphagia in patients with oropharyngeal cancer: clinical and functional results. J Clin Oncol. 2010;28(16):2732-8.

804. Hunter KU, Lee OE, Lyden TH, Haxer MJ, Feng FY, Schipper M, et al. Aspiration pneumonia after chemo-intensity-modulated radiation therapy of oropharyngeal carcinoma and its clinical and dysphagia-related predictors. Head Neck. 2014;36(1):120-5.

805. Reddy PD, Yan F, Nguyen SA, Nathan CO. Factors Influencing the Development of Pneumonia in Patients With Head and Neck Cancer: A Meta-analysis. Otolaryngol Head Neck Surg. 2021;164(2):234-43.

806. Simon SR, Florie M, Pilz W, Winkens B, Winter N, Kremer B, et al. Association Between Pharyngeal Pooling and Aspiration Using Fiberoptic Endoscopic Evaluation of Swallowing in Head and Neck Cancer Patients with Dysphagia. Dysphagia. 2020;35(1):42-51.

807. Ku PK, Vlantis AC, Leung SF, Lee KY, Cheung DM, Abdullah VJ, et al. Laryngopharyngeal sensory deficits and impaired pharyngeal motor function predict aspiration in patients irradiated for nasopharyngeal carcinoma. Laryngoscope. 2010;120(2):223-8.

808. Molfenter SM, Steele CM. The relationship between residue and aspiration on the subsequent swallow: an application of the normalized residue ratio scale. Dysphagia. 2013;28(4):494-500.

809. Meyer TK, Pisegna JM, Krisciunas GP, Pauloski BR, Langmore SE. Residue influences quality of life independently of penetration and aspiration in head and neck cancer survivors. Laryngoscope. 2017;127(7):1615-21.

APPENDIX 1: P-HRM WITH AND WITHOUT IMPEDANCE STUDIES IN ADULT DYSPHAGIC COHORTS

Study	Objectives/Methodology	P-HRM/P-HRM-I Equipment/ Methodology	Salient Results/Conclusions
1. Taira and colleagues, 2021 (598)	To correlate severity of Parkinson's disease (PD) with swallowing (n=51).	Starr Medical solid-state catheter, 20 circumferential pressure sensors TA 5 x reps of saliva swallows Pressure measures P-HRM with FEES to confirm position of catheter in the pharynx and identify the pressure sensors within the anatomical regions.	Patients with severe PD demonstrated reduced velopharyngeal and oropharyngeal pressures and incomplete UOS opening and contraction.
2. Kallusky and colleagues, 2020 (605)	To evaluate pharyngeal pressures during swallowing in adults with unilateral cleft lip and palate (n=10)	Medical Measurement Systems (MMS) solid-state catheter, 20 unidirectional pressure sensors	When compared with healthy controls, the ten patients with unilateral cleft lip and palate showed reduced velopharyngeal closure pressures and reduced velopharyngeal and tongue durations.

		No TA 10 x reps of each 2 and 5 mL of water Pressure measures P-HRM alone	The reduced tongue base pressure durations may be a compensatory response to assist with bolus movement over the tongue base and towards the UOS, to impede nasal regurgitation of the bolus.
3. Kunieda and colleagues, 2020 (607)	To assess the association swallowing is older patients with sarcopenic dysphagia following hospital admission	ManoScan solid-state catheter, 36 circumferential sensors No TA 3 x reps of 3 mL thin and thick fluids Pressure measures P-HRM alone	Older patients with sarcopenia demonstrated, reduced mesopharyngeal contractility and UOS dysfunction characterised by a shorter UOS RT and increase UES IRP.
4. Lee and colleagues, 2020 (634)	Chin down manoeuvre healthy and (n=20) heterogenous dysphagic (n=64) cohorts	Sandhill Scientific solid-state catheter, 32 circumferential sensors 5 mL of thin and thick fluids (honey consistency)	No significant differences in chin-down posture between dysphagic and healthy cohorts, or thin and thick liquids.

		Pressure measures P-HRM alone	
5. Schaen-Heacock et al 2020 (28)	Compare swallowing function in patients with radiation-associated dysphagia (n=13) and late-radiation associated dysphagia (n=8) following HNC treatment	ManoScan solid-state catheter, 36 circumferential sensors TA 1cc of liquid Pressure measures P-HRM alone	Both HNC patients radiation associated dysphagia presented with reduced pharyngeal pressures and duration. Nil differences between the two groups. Future studies should identify if reduced pressures and durations correlate with inefficient bolus propulsion and associated increased risk of airway invasion.
6.Suh et al 2019 (596)	Establish standardized pressure measures to indicate suitability of commencement of alternative tube feeding on Motor Neuron Disease (MND) Healthy participants (n=20) compared with MND (n=41), 7 of who had tube feeding	Sandhill Scientific solid-state catheter, 36 circumferential pressure sensors TA 5ml water, 2 repeats Pressure parameters	Velopharyngeal, tongue base, lower pharynx and cricopharyngeal regions were significantly reduced in the MND group compared to the healthy participants. The velopharyngeal and low pharyngeal pressures were significantly different from the fully oral and tube feeding groups of MND patients.

		VFSS/P-HRM within 2 day interval	
7.Jones et al 2018 (597)	Utilised artificial neural networks (ANN) to differentiate between early Parkinson's disease (PD) (n=31) and healthy participants (n=31)	ManoScan solid-state catheter , 36 circumferential pressure sensors TA 2cc, 10cc, sip of thin fluids Pressure measures Simultaneous VFSS/P-HRM	Pressure within the mesopharynx and UOS was greater in patients diagnosed with early Parkinson's disease compared to healthy controls. Early identification of altered pressure patterns may determine suitability for preserving swallow function.
8.Schar et al 2018 (1)	Swallowing changes in patients diagnosed with moderate-severe OSA who had surgical intervention (n=12) compared with healthy participant (n=10)	Medical Measurement Systems (MMS) solid-state catheter, 32 unidirectional pressure sensors, 16 impedance segments TA 5, 10, 20ml thin, extremely thick fluids, 3 repeats	Increased hypopharyngeal intra-bolus pressure associated with reduced UOS luminal opening with increased bolus volumes. Surgical management of OSAS may impact swallowing function as evidenced by altered neuromodulation to bolus volume. Pre- and post-surgical intervention study is required.

		Pressure and impedance measures Simultaneous P-HRM/SSQ Unspecified follow-up VFSS (n=6) in patients with reported symptomatic dysphagia	
9.Sung et al 2018 (600)	P-HRM as an assessment of swallowing in acute stroke (n=91)	Sandhill Scientific solid-state catheter, 36 circumferential pressure sensors, 12 impedance segments TA 5ml of saline, 10 repeats Pressure and impedance measures P-HRM alone	Those patients (n=36/91) with an impaired swallowing pattern were associated with shorter UOS opening, reduced pharyngeal contractile integral and basal UOS tone. Describes a swallowing assessment program combining clinical observations, the Water Swallow Test and the use of P-HRM in the assessment of swallowing and appropriate dietary management in acute stroke.
10. Szczesniak and	Investigate the impact of pharyngeal contractility on intra-bolus distension	MMS solid-state catheter with 25 unidirectional	Intra-Bolus Pressure demonstrated good sensitivity and specificity indicating a PEJ stricture with

colleagues, 2018 (561)	pressure (IBP) where IBP is a surrogate for pharyno-oesophageal juncture (PEJ) stricture HNC (n=52) patients with reported dysphagia requiring endoscopic dilations	pressure sensors and 12 impedance segments TA 5ml thin liquids Pressure and impedance measures Simultaneous P-HRM/VFSS	adequate pharyngeal contractility (peak pharyngeal pressure >57mmHg).
11. Lee and colleagues, 2017 (599)	Correlate abnormal findings on P-HRM AND VFSS to identify aspiration risk factors in patients with ischaemic stroke (n=36)	ManoScan solid-state catheter, 36 circumferential pressure sensors TA 5ml water, 5 repeats Pressure measures P-HRM and VFSS with one day interval	Mesopharyngeal and hypopharyngeal contractile integrals in stroke patients with pyriform sinus residue were significantly lower than those in patients without pyriform sinus residue. Shorter relaxation time interval of the UOS during swallowing is associated in those patients with observed aspiration compared with those patients without aspiration.

12. O'Rourke and colleagues, 2017 (582)	Correlate the pharyngeal contractile integral (PhCI) with VFSS MBSImp rating scale in a heterogenous population (n=36)	ManoScan solid-state catheter, 36 circumferential pressure sensors TA Pressure measures Increased liquid volumes and consistencies Simultaneous P-HRM/ VFSS	PhCI was correlated with MBSImp pharyngeal total (PT) score, indicating worse swallowing impairment. Increased PhCI was associated with less airway invasion scores overall. PhCI should be evaluated with measures of IBP as a marker of UOS function.
13. Park and colleagues, 2017 (635)	To determine if P-HRM measures can determine feeding method and predict risk of aspiration pneumonia in patients with dysphagia (heterogenous) (n=120)	ManoScan solid-state catheter, 36 circumferential pressure sensors TA Pressure measures 5ml water, 5 repeats VFSS and P-HRM with one week interval	Reduced velopharyngeal maximal pressure and shorter UOS relaxation duration was associated in those patients who were in the non-oral feeding group with moderately severe and severe dysphagia and identified as significant predictors for the development of aspiration pneumonia.

14. Park and colleagues, 2017 (584)	Identify P-HRM measures that differentiate the dysphagia cohort (heterogenous) (n=75) from healthy cohort (n=28)	ManoScan solid-state catheter, 36 circumferential pressure sensor TA Pressure measures 5ml water, 5 repeats P-HRM and VFSS with 2 day interval	Velopharyngeal and tongue base maximal pressure and UOS relaxation duration and relaxation resting pressure were significantly lower in the dysphagia group compared with healthy controls. Negative correlation of velopharyngeal maximal pressure and dysphagia. Negative correlation of tongue base maximal pressure and dysphagia is consistent with Knigge and Thibeault 2016
15. Pinna and colleagues, 2017 (601)	To determine P-HRM based parameters of patients who had dysphagia associated with peripheral unilateral vagal paralysis (n=16)	ManoScan circumferential pressure sensors Pressure measures 5ml water, 10 repeats P-HRM alone	Velopharyngeal pressures were hypotonic in half of the patients with only one-third presenting with compromised UOS relaxation. Dysphagia was associated with low pharyngeal pressure generation.
16. Cock and colleagues, 2016 (591)	To determine if UOS admittance (inverse of nadir impedance) and 0.2s integrated relaxation pressure (IRP) can predict UOS dysfunction in patients with	MMS solid-state catheter, 32 unidirectional pressure sensors ,16 impedance segments TA	Reduced UOS admittance and increased UOS IRP in MND patients compared with healthy group. Increased IRP in MND patients compared with healthy cohort, but similar values in CPB patients.

	cricopharyngeal bar (CPB)(n=11) and motor neuron disease (MND) (n=16) compared with a healthy cohort (n=66)	Pressure and impedance measures 5ml thin and viscous, 3 repeats Unspecified radiology/P-HRM interval	UOS Admittance is able to distinguish UOS dysfunction in two differing patients groups when compared to a healthy cohort.
17. Jones & Ciucci, 2016 (26)	Early and mid-stage of Parkinson's disease (n=26) compared with healthy cohort (n=26)	ManoScan solid-state catheter, 36 circumferential pressure sensors TA Pressure measures Simultaneous P-HRM/VFSS	VFSS parameters (MBSImp and PAS) did not differentiate PD group from healthy group. Velopharyngeal pressure and variability of velopharyngeal pressure of the P-HRM measures and Q6 of the SSQ "Do you have difficulty swallowing your saliva?" were able to differentiate the PD from the healthy groups. P-HRM and SSQ may be able to identify the subtle changes in swallowing function in early- and mid-stage PD.
18. Knigge & Thiebault, 2016 (107)	Compared tongue base pressures via P-HRM and observed vallecular clearance	ManoScan solid-state catheter ,36 circumferential pressure sensors TA	No significant association between mean peak HRM measures and observed vallecula residue.

	via VFSS in dysphagic cohort (n=37)	Pressure measures 1ml, 10ml saline P-HRM/VFSS within 45 day interval	Observed complete/incomplete tongue retraction were significantly associated with tongue base measures. Vallecula clearance is likely multifactorial.
19. Lippert and colleagues, 2016 (602)	To correlate P-HRM measures with a "functional" swallowing in patients following total laryngectomy (n=6)	ManoScan solid-state catheter with 36 circumferential pressure sensors TA Pressure measures 5, 10, 20 cc water, 3-5 repeats Healthy controls 10cc water only, 3-5 repeats P-HRM/SSQ	Increased velopharyngeal pressure duration, reduced mesopharyngeal pressure, UOS pre-opening and post closing pressures were lower in the TL group when compared with healthy controls. Mesopharyngeal maximum pressure reduced with increased volume. Increased velopharyngeal pressure duration and total swallow duration to assist in efficient bolus clearance reflecting the distinct function of the neo-pharynx in the TL group.
20. Park and colleagues, 2016	To correlate P-HRM measures with VFSS observations in a heterogenous dysphagic group (n=40)	ManoScan solid-state catheter , 36 circumferential pressure sensors	Velopharyngeal maximal pressure with a cut-off value above 178.8 mmHg showed high sensitivity and specificity for airway invasion.

(585)		TA Pressure measures 5ml thin, 2 repeats VFSS and P-HRM, within same day-3 day interval	Nadir UOS pressure duration was associated with pyriform sinus residue with moderately to high sensitivity and specificity. Tongue base contraction duration was associated with vallecula residue with moderately to high sensitivity and specificity.
21. Zhang and colleagues, 2016 (603)	To characterize P-HRM measures of swallowing in patients who had a total laryngectomy (TL) (n=30). Specifically, to determine if (1) hypopharyngeal contractility is reduced and/or PEJ resistance is increased, (2) dilatation improves dysphagia, and (3) whether symptomatic improvement correlates with reduced PEJ resistance (dilatation group n=5)	MMS solid-state catheter with 25 unidirectional pressure sensors and 12 impedance segments TA Pressure and impedance measures 2, 5 and 10ml liquid Simultaneous P-HRM/ VFSS/SSQ	TL group demonstrated lower hypopharyngeal contractility pressure and increased hypopharyngeal intra-bolus pressures when compared to a healthy group. Hypopharyngeal intra-bolus pressure increased with increased volume in the TL group. Hypopharyngeal intra-bolus pressure, a marker of PEJ outflow obstruction, was strongly associated with SSQ score. Hypopharyngeal contractility was not strongly associated with SSQ. Hypopharyngeal intra-bolus pressure and associated SSQ scores reduced post PEJ dilatation.

22. Ferris and colleagues, 2015 (581)	To correlate pre-swallow pharyngeal bolus presence on VFSS with P-HRM measures in a heterogenous dysphagia cohort (n=40) compared with control group (n=8)	MMS solid-state 25 channel catheter, unidirectional pressure sensors, 12 impedance segments TA Pressure and impedance measures 5 and 10ml liquids Simultaneous P-HRM/VFSS	Patients with pre-swallow bolus presence to the pyriform sinus had significantly increased pharyngeal and UOS impedance measures correlating with reduced pharyngeal distension pressure and UOS opening, respectively compared with those patients without pre-swallow bolus presence to the pyriform sinus. Bolus Presence Time (BPT) was increased in the dysphagia group compared with healthy controls. There was reduced time from bolus distension within the hypopharynx to pharyngeal contraction, (represented by short Distension-Contraction Latency (DCL)) compared with healthy controls. Pre-swallow bolus transit to the pyriform sinus on VFSS was associated with increased Swallow Risk Index (SRI).
23. Szczesniak and colleagues, 2015	Investigated the reliability and validity of AIMplot analysis in Head and Neck Cancer (HNC) patients (n=16) following radiotherapy with controls	MMS solid-state 25 channel catheter, unidirectional sensors, 12 impedance segments TA	SRI via P-HRM was elevated in patients who had observed aspiration on VFSS. The post-swallow residue integrated ratio was moderately consistent with observed residue on VFSS.

(572)	Specifically, to determine the association of airway invasion on VFSS with the SRI via P-HRM; and observed pharyngeal residue with a measure of post swallow residue using P-HRM.	Pressure and impedance measures 5ml thin liquids Simultaneous P-HRM/VFSS	Post-swallow residue calculation is based on the ratio of the nadir impedance/impedance and integrated within a defined 0.25 seconds after the pharyngeal peak pressure. A post-swallow residue cut-off value of 300 is indicative of abnormal residue.
24. Lee and colleagues, 2014 (563)	To determine whether abnormal impedance measures would correlate with observed pharyngeal residue on VFSS in a largely stroke dysphagia group (n=10) and compared with healthy participants (n=26). In addition, to determine pharyngeal pressure patterns in the dysphagia cohort.	Sandhill Scientific solid-state catheter, 25 circumferential and 7 unidirectional pressure sensors, 4 impedance segments TA Pressure and impedance measures 5ml saline, 10 repeats Unspecified VFSS and P-HRM interval	Pharyngeal residue on VFSS and detection of a linear vs “stasis” impedance pattern through the pharyngo-oesophageal segment correlated 100%. Pharyngeal contraction duration was significantly reduced compared with controls. Pharyngeal residue observed on VFSS was further distinguished through P-HRM pressure and timing measures in 2 patients.

25. Omari and colleagues, 2014 (154)	To assess UOS relaxation and opening mechanisms across VFSS and P-HRM analysis in a motor neuron disease group (n=11).	Two MMS solid-state catheters: 25 unidirectional pressure sensors, 12 impedance segments and 32 unidirectional pressure sensors, 16 impedance segments TA Pressure and impedance measures 5ml/10ml saline, 5 repeats Unspecified VFSS and P-HRM interval	Changes observed in motor neuron disease in UOS presented with an overall lower pressures: lower pre-relaxation pressures and post relaxation pressures. Maximum UOS Admittance (UOS luminal diameter) during was significantly reduced in MND patients compared with controls. Increased UOS duration in MND group compared with controls. UOS Admittance of 5-15 mS defined UOS occlusion. Increasing UOS admittance is defined as >10mS/s, which correlated with reduction of impedance. Decreasing UOS admittance is defined as < -1.5mS/s, which correlates with increasing impedance.
26. Geng and collagues, 2013 (586)	Utilised artificial neural network analysis of P-HRM measures to distinguish dysphagia compared (n=61) with healthy participants (n=16) using two methods of pressure and timing analysis; 2-dimensional primarily based on single sensor recordings	ManoScan solid-state catheter, 36 circumferential pressure sensors TA Pressure measures 1cc-20cc of thin-pudding.	Both 2-D and 3-D pressure and timing data analysis overall produced accurate measures to correctly identify disordered vs healthy swallows. 3-D P-HRM analysis allowed for more accurate measures of the UOS and the hypopharynx. 2-D and 3-D demonstrated comparable accuracy for velopharyngeal measures.

	compared with 3 dimensional recordings using the pressure sensors within the region	Unspecified VFSS or FEES/P-HRM interval	
27. Hoffman and colleagues, 2013 (580)	Utilised artificial neural network analyses to correlate P-HRM measures with MBSImp measures in heterogenous dysphagia group (n=30)	ManoScan solid-state catheter, 36 circumferential pressure sensors TA Pressure measures 5 and 10ml, self selected sip of thin, mildly, moderately thick liquids Simultaneous P-HRM/VFSS	Deviations in P-HRM measures correlated with MBS measures. Patients with low PhCI had worse MBSImp pharyngeal total (PT) score, indicative of worse swallowing impairment; and worse airway invasion scores.
28. Hoffman and colleagues, 2013 (30)	Utilised artificial neural network analyses to correlate pressure and impedance measure with aspiration observations on VFSS in a heterogenous dysphagia group (n=25)	MMS solid-state catheter, 25 unidirectional pressure sensors with 12 impedance segments TA	Pressure measures produced greater accuracy when distinguishing safe, penetration or aspiration swallows than impedance measures. Combined pressure and impedance measures produced the greatest accuracy. Maximum velopharyngeal pressure, velopharyngeal pressure integral and UOS rise time provided the

		Pressure and impedance measures 5 and 10ml liquid, semisolid and solid Simultaneous P-HRM/VFSS	highest accuracies distinguishing unsafe (penetration or aspiration) from safe swallows.
29. Lan and colleagues, 2013 (633)	Using P-HRM measures with patient reported outcomes compared standard therapy (n=15) with modified balloon dilatation and standard therapy (n=15) in patients with brainstem stroke	Sierra Scientific solid-state catheter, 36 circumferential pressure sensors TA Pressure measures 3ml water, thick liquid and paste, 3 repeats Unspecified VFSS/P-HRM interval, Functional Oral Intake Scale (FOIS)	Modified dilatation with standard therapy demonstrated increased pharyngeal contractility and UOS relaxation and near normal UOS resting pressure with feeding tube removal in 12/15 patients. In the standard therapy group pharyngeal contractility increased for water and thick liquid, but not for paste with nil improvement in UOS relaxation. 2/15 patients had feeding tube removal.
30. Lee and colleagues, 2012	Case study of a patient with Huntington's disease who reported symptoms consistent	Sandhill Scientific solid-state catheter, 32 pressure	Irregular contraction of the velopharynx, simultaneous contraction between the velopharynx

(558)	with oropharyngeal and oesophageal dysphagia	sensors and 4 impedance segments 5ml saline/viscous, 10 repeats Unspecified P-HRM/VFSS interval	and mesopharynx and impaired bolus transit through the pharyngooesophageal segment.
31. Lee and Lee, 2012 (606)	Case study of a 61 YO complaining of dysphagia symptoms.	ManoScan solid-state catheter Pressure and impedance measures 5ml water, 100ml multiple rapid swallow Unspecified P-HRM/VFSS interval	Shorter UOS relaxation and elevated intra-bolus pressure, which worsened with 100ml multiple rapid swallow test. Increased intra-bolus pressure was correlated across the observed cervical osteophyte on VFSS. VFSS demonstrated reduced UOS opening and pharyngeal residue.
32. Omari and colleagues, 2012 (583)	P-HRM measures investigating the impact of bolus volume and viscosity in heterogenous dysphagia group (n=40)	MMS solid-state catheter, 25 unidirectional pressure sensors, 12 impedance segments TA	Pharyngeal peak pressure increased with increased volume. UOS intra-bolus pressure and UOS resistance increased with increased viscosity.

		Pressure and impedance measures 5,10ml liquid, semisolid/ solid Simultaneous P-HRM/ VFSS	Liquids, regardless of 5 or 10ml volume, oppose to semisolids was associated with increased Swallow Risk Index (SRI), a global measure of swallow function. The SRI, P-HRM measures demonstrated high agreement with observed airway invasion on VFSS.
33. Omari and colleagues, 2011 (567)	Determine pressure and impedance measures of dysphagia group with suspected aspiration (n=20) compared to controls.	MMS solid-state catheter, 25 unidirectional pressure sensors , 12 impedance segments TA Pressure and impedance measures 5 and/or 10ml liquid, semisolid and solid Simultaneous P-HRM/VFSS	Dysphagia patients with observed aspiration on VFSS, had reduced pharyngeal peak pressures, shorter time from bolus distension to pharyngeal contraction and increased bolus presence time. Dysphagia patients with pharyngeal residue on VFSS presented with increased bolus presence time. Swallow Risk Index with a cut-off value of 15 or more is highly consistent with observed aspiration on VFSS.

Abbreviation: TA = topical anaesthesia

APPENDIX 2: P-HRM-I CORE METRICS

APPENDIX FIGURE 1: VFSS AND CORRESPONDING P-HRM OF A 10 ML THIN LIQUID SWALLOW IN A HEALTHY CONTROL. **A: Lateral VFSS image shows the 8Fr catheter in the trans-nasal position spanning the velum to the UES, at rest. B: P-HRM pharyngeal pressure-topography plot of a complete swallow. Boxes represent regions for the velopharyngeal (VCI), mesopharyngeal (MCI) and hypopharyngeal (HPCI) contractile integrals. The corresponding regions are seen on the adjacent VFSS image (the pharyngeal contractile integral (PhCI) is the mean of the VCI, MCI and HPCI). C: Hypopharyngeal derived metric, Intra-Bolus Pressure (IBP), is represented as the peak of admittance of bolus movement (in pink). D: UES derived metrics, relaxation time (UES RT), opening extent (UES Maximum Admittance) and pressure (UES IRP) are shown in relation to UES pressure (in black) and bolus movement (in pink). E: UES Relaxation Time (UES RT) is the duration from UES relaxation to UES contraction, represented by the yellow vertical lines on hypopharyngeal and UES admittance/pressure graphs and by the yellow dots on the pressure topography plot. Figure (800)**

APPENDIX 3: PUBLISHED PAPERS

APPENDIX 4: DISCUSSION FROM POST-HNC TREATMENT COHORT (CHAPTER 8)

VFSS Outcomes of Aspiration and Residue

High rates of airway penetration and aspiration were observed in participants following HNC treatment. Utilising VFSS-derived measures, PAS scores demonstrated the depth of airway invasion and response (455). A PAS ≥5 is indicative of either silent penetration to the vocal folds without a cough response (PAS =5) or aspiration (PAS ≥6), with higher PAS scores associated with decreasing response. In the post HNC treatment cohort, 72% (10/14) presented with a PAS ≥5, with 57% presenting with a PAS ≥6. Unsurprisingly, these increased PAS values were significantly associated with increased DIGEST Safety Grades (PAS modified by frequency and amount) and DIGEST Summary Grades, which indicates a greater severity of dysphagia. Reduced response to penetration or aspiration can indicate sensory dysfunction (explained in *Section 1.1.3*) where silent penetration (PAS =5) suggests impairment of the internal branch of the superior laryngeal nerve sensory receptors at the true vocal folds, whereas aspiration (PAS ≥6) with impaired response suggests dysfunction of the recurrent laryngeal nerve receptors below the true vocal folds (148). Recently, it was reported that laryngopharyngeal sensory neuropathy, defined as an absent response to palpation of the aryepiglottic folds or traversing the vocal folds without eliciting a cough reflex, has a high prevalence in post-HNC treatment participants requiring alternative nutritional support via enteral feeding (801). In the post-HNC treatment cohort a high incidence of silent penetration to the vocal folds or aspiration was observed suggesting an impairment of the laryngeal sensory receptors (148), which may correspond with observed laryngopharyngeal sensory neuropathy, which has been reported in post-HNC treatment (801).

The high rates of airway penetration and aspiration found in this study are consistent with previous publications (385, 802), but higher than some studies who reported lower aspiration rates between 24-31% at 12 months post treatment in larger cohorts (n >60) (381, 803). This difference may be reflective of a recruitment bias in this retrospective analysis, as data was obtained from patient referred for VFSS on clinical grounds suspecting aspiration. Nevertheless, aspiration has significant clinical and quality of life implications as penetration/aspiration of saliva, liquids or foods below the vocal folds into the lungs can lead to aspiration pneumonia (235). Aspiration pneumonia is reported to occur in up to 20% of patients following oncologic treatment of HNC (252, 382, 804), and accounts for 19% of non-cancer related deaths in this cohort (379). Interestingly, although a recently published systematic review demonstrated that aspiration identified on VFSS was associated with increased risk of the development of pneumonia with univariate analysis, it was not an independent factor on multivariate analysis (805).

Vallecula residue was observed in 85% (11/13) of the post-HNC treatment cohort, and pyriform sinus residue in 54% (7/13). In a recently published systematic review, the pharyngeal residue parameter was shown to increase in frequency over time: 47% at < 6 months post-HNC treatment to 74% at > 6 months post-treatment (366). In our study, a significant correlation between valleculae and pyriform sinus residue with residue (DIGEST Efficiency Grade) on VFSS was demonstrated. However, only pyriform sinus residue was significantly associated with DIGEST Safety and Summary Grades. The findings of a significant relationship of pyriform sinus residue with aspiration are consistent with previous publications evaluating dysphagia in HNC patients, and following radiotherapy treatment (806, 807). It is unknown whether this has a causal relationship; one proposed explanation is the close proximity of the pyriform sinus to the laryngeal vestibule resulting in overflow from the pyriform sinus into the airway (806). In dysphagic patients (using VFSS), aspiration associated with pharyngeal residue has been reported to have an increased risk with thin liquid swallows during subsequent clearing swallows (734, 783, 808). These findings differ to those from Pisegna and colleagues (2020) who found a weak relationship between residue and timing of penetration and aspiration events in a post-HNC treatment cohort. However, this may be attributed to the use of a non-validated measure of residue (472). Nevertheless, pharyngeal residue itself has demonstrated clinical importance, with significant associations with poorer patient perceived quality of life (809) and utility in swallow screening assessments (405).

APPENDIX 5: SUPPLEMENTARY ANALYSIS OF THE P-HRM-I CORE METRICS FOR THE PRE- AND POST-TONGUE BASE AUGMENTATION PROCEDURE

The median values of the P-HRM-I metrics pre- and post-procedure are presented in Table 2 for 5 mL and 10 mL volume of thin liquids.

APPENDIX TABLE 2: P-HRM-I CORE METRICS PRE- AND POST-TONGUE BASE AUGMENTATION PROCEDURE WITH 5- AND 10-ML VOLUMES OF THIN LIQUIDS

P-HRM-I Core Metrics (Median, IQR)					
Metric	**Volume (mL)**	**IDDSI Level**	**Pre-Surgery**	**Post-Surgery**	**p value**
Pharyngeal Contractile Integral PhCI mmHg.cm.s	5	0	63 [35, 192]	70 [27, 182]	p = 0.75
	10	0	53 [28, 250]	55 [25, 151]	p = 0.23
Velopharyngeal Contractile Integral VCI mmHg.cm.s	5	0	17 [17, 83]	21 [-0.6, 52]	p = 0.12
	10	0	12 [3, 108]	2 [-2, 38]	p = 0.35
Mesopharyngeal Contractile Integral MCI mmHg.cm.s	5	0	16 [1, 45]	12 [2, 49]	p = 0.75
	10	0	19 [2, 62]	16 [0, 49]	p = 0.08
Hypopharyngeal Contractile Integral HPCI mmHg.cm.s	5	0	28 [19, 78]	40 [21, 76]	p = 0.60
	10	0	29 [20, 80]	34 [18, 76]	p = 0.89
Hypopharyngeal Intra-Bolus Pressure IBP mmHg	5	0	6 [0.2, 16]	7 [3, 9]	p = 0.75
	10	0	6 [-2, 15]	3 [1,11]	p = 0.89
UES Integrated Relaxation Pressure UES IRP mmHg	5	0	6 [-2, 16]	3 [-3, 14]	p = 0.17
	10	0	3 [-2, 4]	2 [-3, 7]	p = 0.50
UES Maximum Admittance UES Max Ad mS	5	0	4 [2, 4]	4 [3, 4]	p = 0.92
	10	0	4 [3, 4]	4 [3, 5]	p = 0.35
UES relaxation time UES relax time s	5	0	0.6 [0.5, 0.7]	0.5 [0.3, 0.6]	p = 0.17
	10	0	0.6 [0.5, 0.7]	0.7 [0.5, 0.7]	p = 1.0

Additional P-HRM-I Metrics (Median, IQR)					
Swallow Risk Index	5	0	29 [15, 61]	12 [6, 28]	**p = 0.008**
SRI	10	0	17 [13, 193]	52 [7, 130]	p = 0.893
Peak Pharyngeal	5	0	39 [25,76]	50 [33, 88]	p =0.166
Pressure mmHg	10	0	39 [25, 120]	35 [20, 93]	p = 0.138
Bolus Presence	5	0	5 [2, 7]	2 [1,2]	p = 0.075
Time **BPT** s	10	0	5 [3, 7]	2 [1, 4]	p = 0.080
DCL	5	0	0.23 [0.16, 0.28]	0.27 [0.2, 0.33]	p = 0.093
s	10	0	0.23 [0.21, 0.34]	0.26 [0.22, 0.41]	p = 0.197
UESBP	5	0	84 [48,108]	81 [28, 128]	p = 0.917
mmHg	10	0	86 [57, 103]	102 [51, 169]	p = 0.225
UESCI	5	0	637 [256, 734]	381 [268, 656]	p = 0.345
mmHg.cm.s	10	0	530 [315, 655]	593 [294, 657]	p = 0.686
Proximal	5	0	285 [199, 532]	248 [186,267]	p = 0.116
Esophageal Contractile Integral **ProxEsCI** mmHg.cm.s	10	0	274 [166, 426]	266 [172, 310]	p = 0.893

APPENDIX TABLE 3: SUPPLEMENTARY P-HRM-I CORE METRICS PRE- AND POST-TONGUE BASE AUGMENTATION PROCEDURE WITH 5- AND 10-ML VOLUMES OF THIN LIQUIDS

Case	Time	Pharyngeal Contractile Pressures				UOS Relaxation Duration	
		Velo-pharyngeal Contractile Integral *mmHg.s.cm*		Hypo-pharyngeal Contractile Integral *mmHg.s.cm*		UES Relaxation Time *s*	
		5 mL	10 mL	5 mL	10 mL	5 mL	10 mL
1	Pre	24	21	43	47	0.7	0.8
	Post-HA	22	2	54	56	0.5	0.6
2	Pre	85	194	182	112	0.5	0.6
	Post-HA	50	50	142	96	0.2	0.3
3	Pre	83	50	24	21	0.5	0.7
	Post-HA	60	65	53	45	0.3	0.4
4	Pre	10	7	32	29	0.6	0.5
	Post-HA	0	0	27	34	0.6	0.8
5	Pre	10	12	13	22	0.7	0.6
	Post-HA	21	23	19	17	0.7	0.7
6	Pre	0	0	21	19	0.5	0.7
	Post-HA	0	0	23	19	0.5	0.7