Characterising Pharyngeal Swallowing Physiology: Towards Clinical Application of High-Resolution Manometry with Impedance in Children

By

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Thesis Summary

Given the increasing prevalence of oropharyngeal dysphagia in children, it is crucial to investigate the value of novel, quantitative measures in order to advance clinical dysphagia assessment and management. This thesis demonstrates that catheter-based pharyngeal high-resolution manometry with impedance (P-HRM-I) detects contractility, distension and bolus flow timing through the pharynx and upper oesophageal sphincter (UOS) to characterise distinct biomechanical features of swallowing physiology. These quantitative measurements were the investigative focus of this research program. Enhanced characterisation of healthy oropharyngeal swallowing modulation is shown in response to a wide range of bolus conditions, and normative P-HRM-I references have been generated to guide interpretation of OPD pathophysiology. This research demonstrates insights related to technical aspects of manometry, including a clear influence of catheter diameter on P-HRM-I parameters, emphasising the importance of pressure data interpretation in the context of catheter specifications. Another important consideration proved to be the impact of piecemeal deglutition, whereby use of impedance data can enhance selection of swallows for analysis. Exploration of P-HRM-I in children with OPD demonstrated that UOS dysfunction is particularly relevant to symptoms, highlighting the importance of considering and quantifying UOS biomechanics when evaluating OPD. The P-HRM-I parameters may be especially beneficial as future outcome measures of therapeutic interventions, however paediatric P-HRM-I studies present unique challenges regarding test tolerance and protocol compliance. Therefore, it was necessary to explore strategies to optimise the procedure in children and establish the viability of repeat investigations. This research describes a range of factors which influenced data quality and outlines the lessons learned while optimising application of these methods in children. To continue to reveal the most useful clinical contexts for future P-HRM-I application, ongoing exploration of paediatric swallowing pathophysiology is required in larger cohorts, ideally in comparison with other quantitative instrumental methods.

Declaration by Author

I certify that this work does not incorporate without acknowledgment 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. I use the personal pronoun of “our” / “we” where the research reflects the work of the research team as detailed in the publications section, and “I” when drawing on my own experiences and when providing personal conclusions and perspectives.

Signed: Lara Ferris

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First Author Publications During Candidature

Ferris L, Omari T, Selleslagh M, Dejaeger E, Tack J, Vanbeckevoort D, et al. Pressure flow analysis in the assessment of pre-swallow pharyngeal bolus presence in dysphagia. Int J Otolaryngol. 2015; 2015:1-7.

Ferris L, Rommel N, Doeltgen S, Scholten I, Kritas S, Abu-Assi R, et al. Pressure-flow analysis for the assessment of pediatric oropharyngeal dysphagia. J Pediatr. 2016; 177: 279-85.

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. 2017; 128(6):1328-34.

Ferris L, King S, McCall L, Rommel N, Scholten I, Teague W, et al. Piecemeal deglutition, and the implications for pressure impedance dysphagia assessment in pediatrics. J Pediatr Gastroenterol Nutr. 2018; 67(6):713-9.

Ferris L, Omari T. Pharyngeal manometry in pediatric dysphagia assessment. Perspect ASHA Spec Interest Groups. 2019; 4(4):656-82. (Invited review).

Ferris L, Doeltgen S, Cock C, Rommel N, Schar M, Carrion S, et al. Modulation of pharyngeal swallowing by bolus volume and viscosity. Am J of Physiology – Gastrointest Liver Physiol. 2021; 320(1): G43-G53.

Accepted Conference Abstracts during Candidature

Ferris L, Cock C, Doeltgen S, Schar M, Omari T[1]. Bolus Consistency and Modulation of the Pharyngeal Swallow. European Society of Swallowing Disorders Conference, Dublin, Oct 2018 (Oral Presentation).

Omari T, Ferris L, Cajander P, Cock C, Doeltgen S, Rommel N, Savilampi J. A Standardized Test Medium to Detect Bolus-related Modulation during High-Resolution Pharyngeal Manometry. Digestive Diseases Week, Washington DC, May 2018 (Poster Presentation).

Ferris L, King S, McCall L, Rommel N, Doeltgen S, Scholten I, Omari T. Piecemeal Deglutition and the Implications for Pressure Impedance Dysphagia Assessment in Pediatrics. European Society of Swallowing Disorders Conference, Barcelona, September 2017 (Oral presentation).

Ferris L, Schar M, Doeltgen S, Scholten I, Omari T. Effect of Bolus Volume and Catheter Diameter on High Resolution Manometry Impedance Recordings with Pressure Flow Analysis in Healthy Volunteers. European Society of Swallowing Disorders Conference, Milan, Oct 2016 (Poster presentation).

Ferris L, Cock C, Scholten I, Doeltgen S, Rommel N, Omari T. Pressure Flow Analysis and Swallow Variability in Patients with Motor Neurone Disease. European Society of Swallowing Disorders Conference, Barcelona, Oct 2015 (Poster presentation).

Ferris L, Omari T, Selleslagh M, Dejaeger E, Tack J, Vanbeckevoort D, Scholten I, Doeltgen S, Rommel N. Pre-swallow Pharyngeal Bolus Presence in Dysphagia. Australia Scientific & Medical Research Conference, Adelaide, June 2015 (Oral presentation).

Ferris L, Omari T. Swallowing Assessment Using High Resolution Manometry Impedance Analysis. The Sydney Paediatric Feeding and Dysphagia Conference, Sydney, September 2015 (Invited Oral Presentation).

[1] Underlining refers to presenting author.

Ferris L, Kritas S, McCall L, Rommel N, Omari T. Pressure Flow Analysis Correlates with Clinical Measures of Paediatric Dysphagia. European Society of Swallowing Disorders Conference, Brussels, October 2014 (Oral presentation).

Ferris L, Omari T, Selleslagh M, Rommel N. Pressure Flow Analysis for Assessment of Pre-swallow Pharyngeal Bolus Presence in Dysphagia. European Society of Swallowing Disorders Conference, Brussels, October 2014 (Poster Presentation).

Ferris L, Kritas S, McCall L, Rommel N, Omari T. Pharyngeal Swallowing in Children with and without a Manometric Diagnosis of Achalasia. Speech Pathology Australia National Conference, Melbourne, May 2014 (Poster presentation).

Abbreviations List

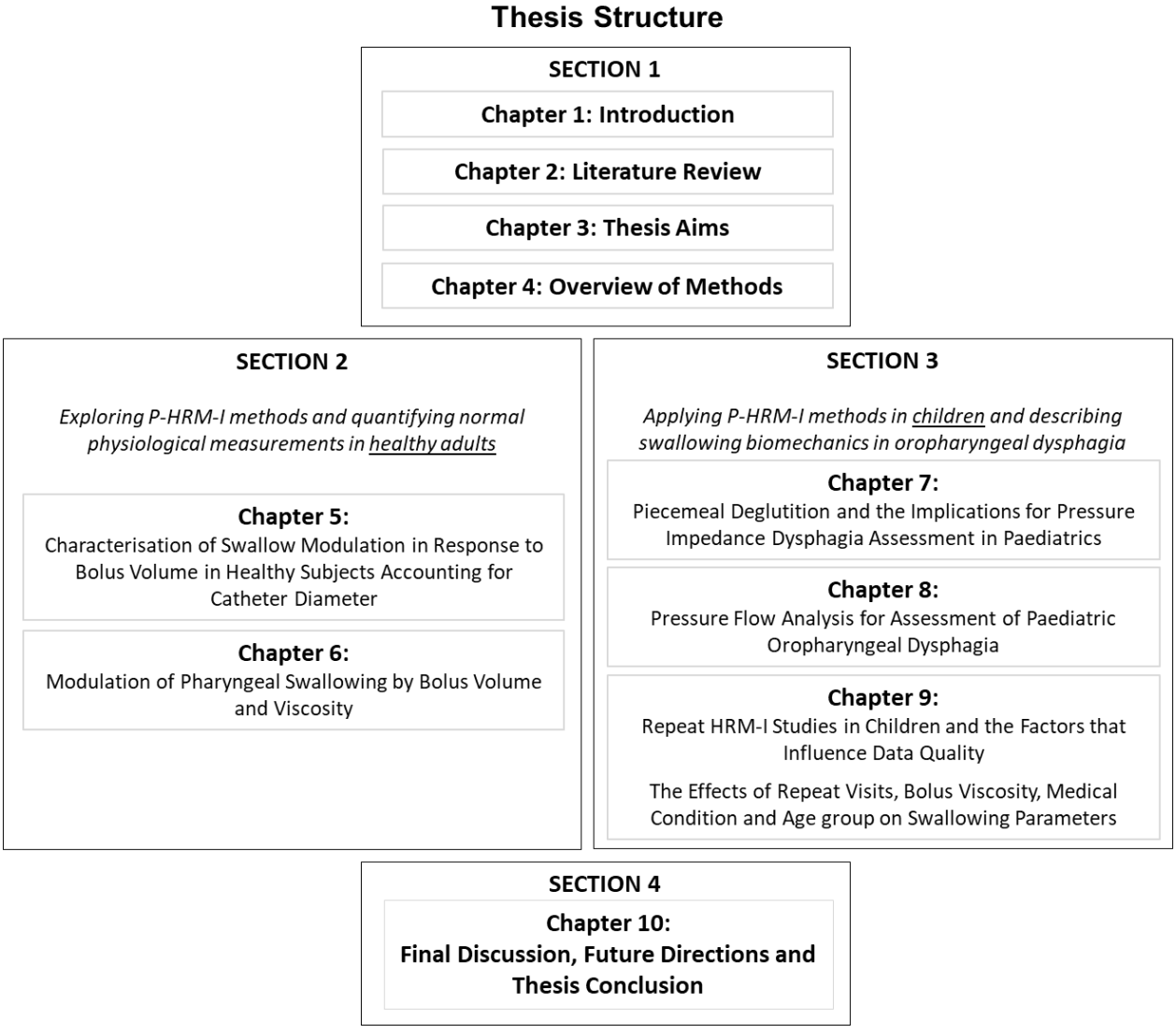
AIMplot	Automated Impedance Manometry plot
AIRWAYcl	Time to airway closure
ALTE	Acute life-threatening event
ANOVA	Analysis of Variance
ASCII	American Standard Code for Information Interchange
BabyVFSSImp©	Baby Videofluoroscopy Swallow Study Impairment Profile
BCR	Bolus Clearance Ratio
BOT	Base of Tongue
BPT	Bolus Presence Time
BP1AEcl	Airway closure relative to bolus reaching UOS
CHARGE	Coloboma, Heart defects, Atresia of choanae, Retardation of Growth, Ear abnormalities
COS	Core Outcome Set
cm	centimetre
CP	Cerebral palsy
CP	Cricopharyngeal/cricopharyngeus
CSA	Clinical Swallowing Assessment
DCL	Distension Contraction Latency
DDS	Dysphagia Disorders Survey
DSS	Dynamic Swallow Study
DMSS	Dysphagia Management Staging Scale
EFT Viscous	Esophageal Function Test commercially available Sandhill Scientific viscous bolus product
EMG	Electromyography
ENT	Ear Nose and Throat
FEES	Flexible Endoscopic Evaluation of Swallowing
FEESST	Flexible Endoscopic Evaluation of Swallowing Sensory Testing
FI	Flow Interval
FOIS	Functional Oral Intake Scale
GOR(D)	Gastro-Oesophageal Reflux (Disease)
GI	Gastrointestinal
hIBP	Hypopharyngeal intra-bolus pressure
HPCI	Hypopharyngeal Contractile Integral
HPT	Hypopharyngeal Transit Time
HREC	Human Research Ethics Committee
HRM	High-Resolution Manometry

HRM-I	High-Resolution Manometry with Impedance
IBP	Intra-Bolus Pressure
IDDSI	International Dysphagia Diet Standardization Initiative
MBSImP™	Modified Barium Swallow Impairment Profile
MCI	Mesopharyngeal Contractile Integral
M FOIS	Modified Functional Oral Intake Scale
ml	Millilitre(s)
MMS	Medical Measurement Systems
mm	Millimetre
mS	Millisiemen
mSv	Millisievert
NaCl	Sodium Chloride
OA	Oesophageal Atresia
OD	Oesophageal Dysphagia
OPD	Oropharyngeal Dysphagia
OPT	Oropharyngeal Transit Time
PAS	Penetration Aspiration Scale
PAm	Maximum Pharyngeal Constriction Area
PAs	Maximum Pharyngeal Area at Rest
PCI	Proximal oesophageal Contractile Integral
PCR	Pharyngeal Constriction Ratio
PD	Piecemeal Deglutition
PES	Pharyngo-esophageal segment
PESdur	Pharyngo-esophageal segment opening duration
PESmax	Pharyngo-esophageal segment maximum diameter
PFA	Pressure Flow Analysis
PhCI	Pharyngeal Contractile Integral
P-HRM-I	Pharyngeal High-Resolution Manometry with Impedance
P-HRM	Pharyngeal High-Resolution Manometry
PNI	Pressure at Nadir Impedance
PP	Peak Pressure
PSIR	Post Swallow Impedance Ratio
ROI	Region of Interest
SBM	Swallow Bolus Medium
SP	Speech Pathologist
SPSS	Statistical Package for the Social Sciences

SRI	Swallow Risk Index
TNIPP	Time from Nadir Impedance to Peak Pressure
TOF	Trache-Oesophageal Fistula
TPT	Total Pharyngeal Transit Time
UOS	Upper Oesophageal Sphincter
UOS BP	UOS Basal Pressure
UOSCI	UOS Contractile Integral
UOS IRP	UOS Integrated Relaxation Pressure
UOS Max Ad	UOS Maximum Admittance
UOS OT	UOS Opening Time
UOS PP	UOS Peak Pressure
UOSRES	UOS Relaxation Pressure
UOS RT	UOS Relaxation Time
VCFS	Velocardiofacial Syndrome
VCI	Velopharyngeal Contractile Integral
VP	Velopharyngeal
VFSS	Videofluoroscopic Swallow Study
WHO	World Health Organisation
yrs	Years
Zn	Nadir impedance

Thesis Structure

The structure of this thesis is presented below. The chapter order corresponds with the overall thesis narrative, rather than the chronology in which the research was conducted. Chapters 1 to 4 are grouped and presented to provide the general background information in Section 1, including the introduction, literature review, thesis aims, and an overview of main methods utilised in this research. The chapters outlining the experimental studies follow and are presented as Section 2 (Chapters 5 and 6, P-HRM-I applied in adults) and Section 3 (Chapters 7 to 9, P-HRM-I applied in children). Section 4 encompasses Chapter 10, which summarises and contextualises the key findings and conclusions of this thesis.

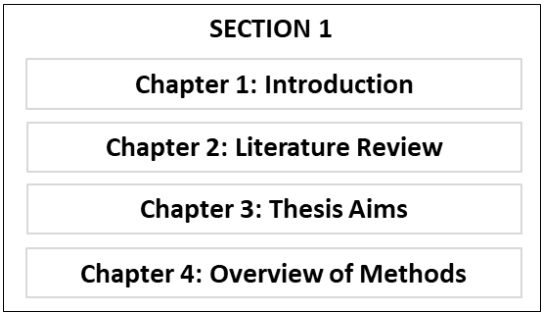


Preface

The vision for this research and the application of its outcomes have evolved throughout my candidature and have also been informed by my personal experiences parenting a child with Trisomy 21, born with oropharyngeal dysphagia (OPD), ongoing at 2 years of age. This thesis presents key findings from two healthy adult cohorts and three paediatric patient cohorts studied with P-HRM-I, which, together, shed light on the potential future clinical value of P-HRM-I pressure flow parameters in the assessment of patients with OPD. The research undertaken during my PhD journey has demonstrated that physiology and pathophysiology can be comprehensively described according to pharyngeal and upper oesophageal sphincter contractility, distension, and bolus flow timing events. Important insights have been gathered regarding the biomechanical features of healthy pharyngeal neuromodulation in response to modified bolus conditions, and key biomechanical markers of dysfunction are highlighted in children with clinical signs and symptoms of OPD. The pressure flow swallow profiles described in this thesis potentially bring these methods a step closer towards clinical application and may guide targeted rehabilitations, compensations and may lead to the development of future therapy innovations. It is my hope that this research will inform the planning of future P-HRM-I studies, particularly in the context of the unique considerations required to optimise the procedure in paediatric populations. In light of the increasing prevalence of paediatric OPD occurring with greater survival rates of prematurity and complex medical conditions (1-4), this thesis serves to contextualise and summarise the findings of this research program and forecast potential applications of the P-HRM-I swallowing assessment. The overarching vision is that new research of this kind may help to advance the professions affiliated with dysphagia assessment and management, with the ultimate goal to improve the quality of life for children with OPD. The true clinical value of P-HRM-I pressure flow parameters requires extensive investigation in healthy cohorts and in patients with OPD, and this research contributes important new information towards this endeavour.

SECTION 1

Section 1 outlines the introduction, literature review, thesis aims, and overview of methods used in this research program.



Chapter 1: Introduction

Feeding disorders can have a devasting impact in childhood. Recent consensus and recognition of an overarching diagnostic terminology defines a paediatric feeding disorder (PFD) as:

> '*impaired oral intake that is not age-appropriate, and is associated with medical, nutritional, feeding skill, and/or psychosocial dysfunction'* (5).

This definition recognises the elaborate interaction among several anatomical (namely, oropharyngeal, craniofacial, and musculoskeletal structures) and physiological systems (namely, central and peripheral nervous systems, cardiopulmonary system, gastrointestinal tract), alongside the psychosocial wellbeing of the caregiver-child dyad (5), and all components need to be considered during assessment and management of paediatric feeding disorders. Swallowing dysfunction (dysphagia) is a major contributor to PFDs and leads to the inadequate bolus passage from the mouth to the stomach. Dysphagia can occur at the level of the oropharynx, upper oesophageal sphincter, and/or incorporate oesophageal dysmotility (6, 7). Consequently, to establish a comprehensive and accurate assessment of dysphagia, a full investigation of the swallowing mechanism may be necessary to identify the underlying pathophysiology. Dysphagia causes increased risk of the movement of food/fluid/gastric contents into the airway below the vocal folds, known as aspiration (6, 7). Aspiration is the primary cause of lung disease in children with oropharyngeal dysphagia (OPD), and subsequent medical issues include potentially life-threatening pneumonia, recurrent chest infections, nutritional and growth deficiencies, and overall reduced quality of life (5, 6, 8). This thesis focuses on children with OPD as it is the main condition under investigation.

The prevalence of OPD in children is increasing. This results from the significant improvements in survival of children with complex medical conditions, especially among those with neurological disease. Reportedly, 80 to 90% of children with neurodevelopmental conditions will experience dysphagia symptoms and adverse health outcomes (9-12). Additionally,

advanced medical technologies have improved premature birth survival which affects an estimated 15 million babies globally each year, and approximately 40% of these children go on to experience PFDs including OPD in some cases (6), an incidence rate four times that of the typically developing infant population (13). The following statement has recently been made:

> *"The range and complexity of [paediatric feeding disorder] problems will continue to challenge the health care, educational, and habilitation/rehabilitation systems because many of these children are now living longer, remaining healthier, and having greater expectations for leading full and productive lives" (6)*.

With this in mind, the need for accurate assessment and effective management of PFDs is emphasised, and the exploration of new assessment techniques and interpretation methods is warranted.

While aspiration can occur with dysphagia of the oropharynx or oesophagus, oropharyngeal dysphagia (OPD) causes the greatest risk of aspiration and adverse health outcomes (14). Instrumental OPD assessments are relied upon to characterise unsafe swallowing features and in paediatric settings the videofluoroscopic swallow study (VFSS) is often referred to as the gold standard (15, 16). Flexible endoscopic evaluation of swallowing (FEES) is also used but comparatively less frequently in children (17), and ultrasound is an emerging technique, with particular relevance to swallowing assessment during breastfeeding (18). In clinical or research practice, all three of these visuoperceptual tests rely on interpretation of image data, which are useful in providing a dynamic evaluation of swallowing and airway structures, bolus movement, and evidence of airway invasion. All three techniques hold unique clinical value, however, they require expert analysis to infer contributing pathophysiology according to anatomical displacement, timing and kinematic measures. Additionally, reports of inter- and intra-reliability vary for these assessments, as is discussed in the sections below. Complementary to these techniques, manometry captures swallowing pressure dynamics and has long been relied upon for oesophageal motility assessment. Acknowledging the intricate pressure dynamics that

occur during pharyngeal deglutition, this thesis explores the potential clinical value of manometry, specifically the objective pressure flow parameters derived by integrated manometry *with impedance*. The parameters derived from this method describe contractility, distension and bolus flow timing features during oropharyngeal swallowing. These parameters are investigated for their ability to enhance descriptions of swallowing biomechanics and physiology.

Manometry is a technique which is increasingly applied in research and clinical contexts of PFDs. In recent years, Australian teaching hospitals have established clinical manometry services for PFDs in paediatric patients through the Royal Children's Hospital in Melbourne, the Lady Cilento Hospital in Brisbane, the Sydney Children's Hospital in Sydney and the Women's and Children's Hospital in Adelaide. This demonstrates the growing medical interest in utilising manometry methods to assess swallowing physiology. If manometry can be optimised for use in the paediatric setting, it may provide an objective technique that complements VFSS, FEES and other clinical swallowing evaluations. The latest catheter technologies are miniaturised and simpler to use, enhancing their potential for more widespread application in paediatric swallowing evaluations. While clinical interest in this technique has increased, the paediatric literature is currently insufficient, and evidence is particularly limited to support P-HRM-I application in children. Therefore, this research program explores several factors relating to P-HRM-I measurements in adults and children to expand the knowledge of its utility in the evaluation of swallowing physiology and detection of pathophysiology in paediatric OPD.

Chapter 2: Literature Review [2]

This thesis explores the application of high-resolution manometry with impedance (HRM-I), a catheter-based assessment which can be applied to pharyngeal or oesophageal swallowing function. This research program specifically focuses on the application of HRM-I in assessment of healthy pharyngeal swallowing physiology and OPD in children, therefore will be abbreviated as pharyngeal HRM-I (P-HRM-I). To provide context for the commonly employed paediatric swallowing assessment methods, this literature review outlines a range of clinical swallowing assessments and instrumental assessment modalities. An important consideration for paediatric evaluation is the anatomical and physiological changes associated with growth and development in infancy and early childhood, which add further layers of complexity to the OPD presentation. Therefore, an overview of the process of typical swallowing development, can be found in Appendix 1.

Most children are impacted by OPD in the context of neurological disorders, cardiopulmonary disorders, anatomic deficits of the airway or pharynx/oesophagus, a history of prematurity, and/or gastrointestinal disorders (8, 17). Several clinical signs of difficulty are immediately recognisable when OPD occurs. These signs include eye watering, coughing, choking, gagging, nasal regurgitation, gastro-oesophageal regurgitation, and changes in breath quality or breathing rate (3, 9, 20-22). Penetration of the airway and/or aspiration causes many of the immediately recognisable signs of swallowing difficulty and can manifest from either OPD, or oesophageal dysphagia, as seen in oesophageal atresia, or primary oesophageal motor disorders such as gastro-oesophageal reflux disease (GORD) and achalasia (23). Subsequent medical issues of aspiration include potentially life-threatening lung disease i.e., pneumonia, recurrent chest infections, bronchiectasis and atelectasis, and this may lead to the need for

[2] The text in this appendix originates from an invited manuscript:

19. Ferris L, Omari T. Pharyngeal manometry in pediatric dysphagia assessment. Perspectives of the ASHA Special Interest Groups. 2019;4(4):656-82. Some wording changes have been made for inclusion in this thesis.

alternative feeding methods, e.g., via nasogastric tube feeding or percutaneous endoscopic gastrostomy feeding (24-26). Other symptoms of dysphagia include chronic vomiting, regurgitation, abdominal pain, dehydration, nutritional and growth deficiencies, difficult and stressful mealtime behaviours and overall reduced quality of life for children (8, 27) and their families (28). Therefore, in the context of obtaining a complete background clinical picture, assessment of oropharyngeal and, where indicated, oesophageal swallowing pathophysiology, is vital for accurate diagnosis of paediatric feeding difficulties and to assess safety of the pharyngeal-airway interface during deglutition (20, 29).

When OPD is suspected, this is usually managed by a multidisciplinary team in which the speech pathologist (SP) plays an important role. Paediatric OPD management includes dietary modifications and/or implementation from a range of therapeutic interventions to optimise deglutitive airway protection, progression of oral skills, and overall growth for a child. In complex cases when dysphagia symptoms may hinder feeding development and when alternative feeding methods via nasogastric tube or gastrostomy are required, a multidisciplinary approach is particularly important to ensure appropriate input from SP, dietitians, specialised nursing staff and paediatricians to optimise outcomes (5, 17, 30-34).

The first step is usually a clinical swallowing assessment (CSA) to ascertain a case history and evaluation of swallowing taken in the clinic setting. In Australia, in children beyond neonatology care, this is almost exclusively conducted by the SP, however, involves occupational therapists or specialist nursing staff in other countries. Swallowing function across a range of age/condition-appropriate food and liquid consistencies is ascertained and signs of unsafe feeding and breathing, such as cough, wet voice, wet breathing, eye watering can be observed and laryngeal penetration, aspiration, and bolus pooling or residue may be postulated. However, instrumental assessment is often recommended to confirm the features suspected during CSA (3, 35-37). Instrumental investigations enable further evidence of OPD symptoms and characterisation of pathophysiology. Each assessment method serves a purpose when characterising a patient's swallowing function. Therefore, to provide the background

information and context for this research program this literature review outlines CSA methods and instrumental assessments, regarding their strengths, limitations, and clinical value for application. As this thesis focuses on P-HRM-I, an overview of manometry use in paediatric populations over the past two decades is included in Section 2.3 (with reference to Appendix 6), with details of the P-HRM-I pressure flow parameters investigated in this research program outlined in Section 2.4.

2.1 Clinical Swallow Assessments

The clinical swallow assessment (CSA) is widely used to assess and manage paediatric OPD as it can be conducted at the hospital bedside or in any community setting. A CSA is used to holistically determine the severity of OPD and its impact on a child's life. The World Health Organization (WHO) states that a comprehensive CSA should evaluate a child's physical and social environment to establish the activity limitations for mealtimes and all underlying physiological deficits which may contribute to their OPD (3, 9). Therefore, a comprehensive CSA encompasses a full case and medical history, examination of a child's posture, oro-motor examination, and follows with feeding trials from a caregiver/therapist to understand a child's mealtime capabilities. Importantly, the CSA also serves to determine whether further instrumental assessment or referral for further multidisciplinary input is required for a child's ongoing care (22).

The CSA is relied upon to determine the immediate efficiency and safety for a child's ongoing oral intake (22). It relies in part on auditory profiling of swallowing sounds using cervical auscultation. Breathing and swallowing sounds are assessed for qualities such as "wet" breathing, promptness of the swallowing response, and placement of the swallow within the breath cycle. As a means of reviewing a child's swallowing status, these features of swallowing are beneficial to the clinician as they facilitate with establishing clinical hypotheses thought to link to swallowing pathophysiology (22). However, identification of these auditory features requires expert training and has varying reports of accuracy, particularly in the absence of an

intact cough reflex (38-42). Overall, the diagnostic test accuracy of a CSA continues to reveal that there is a significant lack of paediatric evidence for reliability, specifically in detecting aspiration (42, 43). The main concern for relying on a CSA to determine patient management is the risk of false negative results, mainly expected to occur in the event of silent aspiration (41). While there is a range of standardised CSA protocols available to clinicians, current clinical practice usually employs informal site-specific assessment protocols for patient management (8). Recommendations have been made to reduce subjectivity and clinical bias during CSA, and include the use of binary scoring within validated rating scales, e.g. Paediatric Eating Assessment Tool 10 (44), the Dysphagia Disorders Survey (45) or the Functional Oral Intake Scale (46). To optimise accuracy during CSA one study showed that liquid swallows provided the most reliable indication of OPD compared to solid swallows (43). Regarding rater reliability, another recent study confirmed that clinical symptoms of aspiration vary greatly, particularly across food textures and from patient to patient (47), however, researchers showed intra-rater reliability is more dependable, likely due to the internal standards clinicians develop in their practice (22, 48).

The CSA remains a vital step in the management of patients with OPD and should not be underestimated for its importance in gathering information regarding the related factors of dysphagia (22) including the need for instrumental dysphagia investigation. The specific CSA measures referred to in the studies in Section 3 of this thesis, are described below.

2.1.1 Dysphagia Disorders Survey

The Dysphagia Disorders Survey (DDS) employed in this research program, is a standardised evaluation tool used internationally for children two years and older (45). The DDS was developed in response to a need for objective, reliable and validated screening tools for children and adults with developmental disability. It is a two-part test which provides a raw score and equivalent disability percentile rank based on binary scored items on the sensorimotor component of feeding competency (food consistencies are considered) and

factors related to OPD (capturing compensatory management and individual effects, e.g. tube feeding and body mass index). See Appendix 2. The higher the DDS score, the greater the feeding dysfunction. The rater is required to observe a child at least five times with each consistency assessed (fluid, non-chewable, chewable). This depends on the child's capabilities and contingency scoring is accounted for within the manual for cases where chewable foods are not taken. Binary scoring reduces subjectivity and inter-rater discrepancies.

The authors suggest that the DDS is a quantitative observation tool with the ability to discriminate swallowing and feeding pathology (45) and this has been supported by independent review of the DDS subcomponents, which showed that the DDS has good clinical utility and sound psychometric properties (49, 50). Specifically, the DDS was validated on a cohort of 626 participants aged between 3-78 years (but is reportedly for use in children from 2 years of age). Content validity and inter-item reliability were addressed during test development, and items with poor inter-item reliability were removed. Inter-rater reliability was good (kappa 0.53-0.71) (45). Whilst the DDS has been shown to discriminate changes in function over time, its authors suggest that an analysis to establish DDS sensitivity to change is required and would increase its usefulness. The DDS requires certification training and has a published manual aiding consistency in its use, further confirming its suitability for research purposes.

2.1.2 Functional Oral Intake Scale

The Functional Oral Intake Scale (FOIS) employed in this research program, is a standardised benchmarking method, which assigns a numerical value to a person's oral intake level, based on the modifications and restrictions implemented in relation to their OPD symptoms. The FOIS was developed to document the impact of dysphagia symptoms on the oral intake in stroke patients with OPD and intended to provide a means to reliably measure change over time (46). The FOIS provides a scale from 1 (patient is nil by mouth) to 7 (person is tolerating a full age-appropriate diet); see Appendix 2. For use in this thesis, correspondence with the creators of

the tool confirmed that it would be appropriate and applicable for use in paediatric research with children over two years of age (who typically have developed the milestone skills for mature textures).

More recently, alterations have been made to the FOIS for use in infants (<12 months), adjusting it to a 5-point scale for developmental appropriateness (51, 52). In the modified FOIS (M FOIS), levels 4-6 are compressed, and the rater determines if introduction of pureed solids before 9 months of age is reached for normal development of oral diet, see Appendix 2. Inter-rater reliability for the M FOIS is high at 0.95 and aspiration status significantly correlated with poorer FOIS scores (52). Adequate reliability and validity were reported for measurements of change over time, particularly for clinical features of calorie intake and consistency of oral intake (52). Similarly, the developers of the tool report high inter-rater reliability (amongst non-experts) and adequate sensitivity to detecting changes in oral intake within a cohort of patients following stroke has been shown (46). Together, these findings support the suitability of FOIS and M FOIS for use in research and clinical contexts and its application in paediatrics is increasing (51-54).

Overall, the CSA plays a vital role in the multimodal and holistic assessment of OPD and in determining the optimal management of a child with dysphagia. The literature suggests that during a CSA, liquid swallowing provides most accurate evidence of OPD compared to solid swallows and binary scoring for documentation of clinical features of OPD reduces subjectivity and provides improved intra- and inter-rater reliability when measuring change over time. While many centres use custom designed CSA evaluations in clinical practice, among the standardised CSA tools there are specific features which influence sensitivity and specificity, i.e., how accurately OPD is detected and how accurately changes in OPD are detected over time. These factors should be considered during CSA selection by the clinician or researcher. In the clinical setting, the CSA ultimately determines whether instrumental assessment is required to substantiate status of airway protection/invasion and the suspected characteristics

of the OPD presentation, particularly in complex cases. An overview of the most commonly employed instrumental assessments is discussed below.

2.2 Instrumental Swallowing Modalities

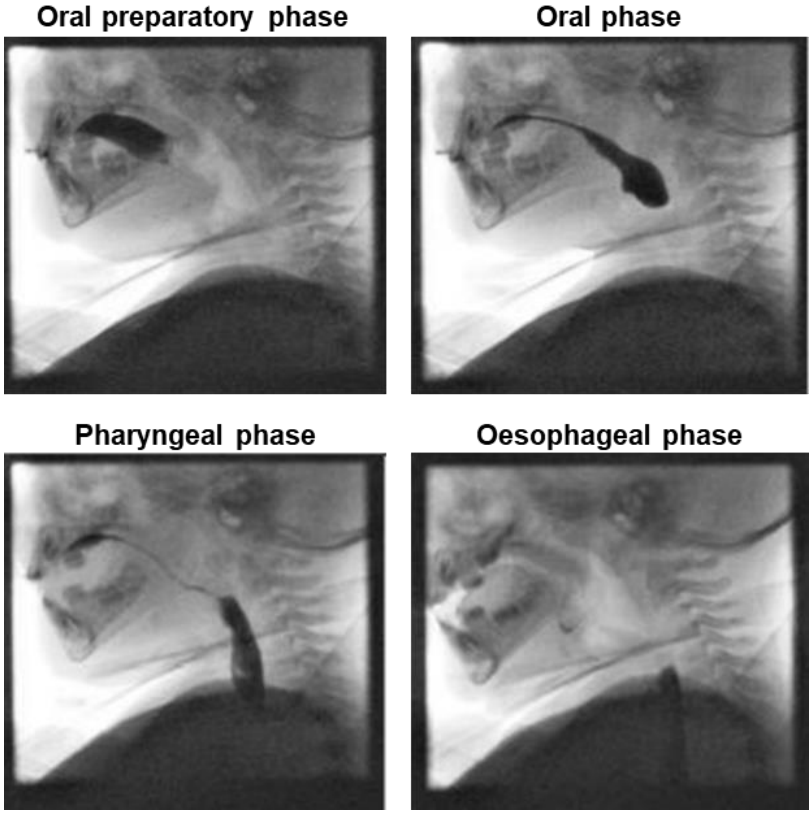
Instrumental swallowing assessments generally involve expensive medical equipment and require specialist skills and expertise to be performed and interpreted. However, the estimated costs of patient hospitalisation with pneumonia far outweigh the cost to perform an instrumental dysphagia assessment. In the context of OPD, instrumental assessment can guide management and minimise adverse health outcomes such as lung health issues or malnutrition. Pneumonia management in the general population leads to several hundred thousand general practice consultations and more than forty thousand hospital admissions in Australia each year (55). A systematic review of the international cost of pneumonia management in young children showed a cost range, dependent on severity of symptoms, of US$5,440 to US$120,000 per child, with a length of stay between 1 to 6 days (56). These figures reinforce the need for accurate dysphagia assessment and treatment, not only to save the individual and their family the immeasurable stress and medical risks associated with chest related illness and malnutrition, but also to reduce the associated health care utilisation and expenditure.

Currently, visuo-perceptual measures VFSS or FEES are the most commonly employed, instrumental assessments in children, and ultrasound is an emerging technique showing benefit in breastfed infants. These tests enable a patient's swallowing impairment to be evaluated according to several factors: observed structural abnormalities; evidence of dysfunction pertaining to known underlying medical conditions; the impact on swallowing safety regarding airway invasion; a range of food and fluid consistencies/flow rates; and swallowing manoeuvres can be tested to optimise swallowing safety and preserve oral intake for a child (9, 19, 57-59). These visuo-perceptual swallowing assessment techniques are outlined below, followed by a detailed discussion of manometry use in swallow assessment.

2.2.1 Videofluoroscopic Swallowing Studies

Videofluoroscopic swallowing studies are widely used to comprehensively assess swallowing function in children (35, 37, 58, 60-63). Fluoroscopy is an imaging method recording sequences of x-ray frames which can be visualised in real time while a patient consumes foods/fluids mixed with radio-opaque contrast such as barium sulphate or water-soluble contrast such as Iohexol solution containing tromethamine and edetate calcium disodium, e.g., Omniopaque™. A lateral view of the oral cavity, oropharyngeal and upper airway anatomy is usually observed with capability to scan into the proximal or whole oesophagus; see Figure 2.1. Frontal frames of anatomy may also add to the assessment. The VFSS enables visualisation of bolus movements relative to swallowing anatomy movements, and uniquely determines a patient's ability to protect their airway before, during and after deglutition. In clinical studies, physiology of swallowing function is inferred from observing oral, pharyngeal and oesophageal (to a lesser extent) stages of swallowing (64). Additionally, based on their observations clinicians may comment on the integrity of the sensory and motor function of the pharynx and larynx (65).

Figure 2.1. ***Videofluoroscopy swallow study and infant swallowing phases***



Note: This figure demonstrates VFSS imaging of the oral preparatory, oral, pharyngeal, and (proximal) oesophageal phases of swallowing. This image was obtained directly from *Batchelor G, McNaughten B, Bourke T, Dick J, Leonard C, Thompson A. How to use the videofluoroscopy swallow study in paediatric practice. Arch Dis Child: Educ & Pract Ed. 2019;104(6):313-20, reproduced with permission.*

A VFSS referral may be made by any treating clinician when there is suspicion of airway invasion with symptoms of choking, coughing, gagging, breath quality changes, work of breathing, gastro-oesophageal reflux (GOR), chest congestion, upper respiratory infections, or a combination of these clinical concerns (66). Considerations for appropriate selection for VFSS relate to: patient mobility and ability to cooperate with correct positioning; tolerance of oral feeding for bolus trials; absence of allergy to barium/iodine contrast, and a calculated risk for exposure to ionising radiation is taken (64). If a patient fits these criteria, the test can usually proceed. In Australia, the VFSS team typically involves a SP to administer the swallow trials and determine swallow safety throughout the assessment, a radiographer to perform the fluoroscopy, a radiologist to finalise the results and a paediatric nurse/allied health assistant

may be present to care for, position the patient, as well as prepare bolus media. Specialised VFSS equipment is generally available in tertiary settings only.

The VFSS is largely considered the most direct and comprehensive assessment of OPD and aspiration risk (35, 37). Swallow and airway structures, bolus movement/clearance, silent aspiration and nasopharyngeal reflux can be observed, which otherwise may be missed during CSA or other instrumental assessment (22, 67). Additionally, penetration/aspiration are observed dynamically in relation to the timepoint of their occurrence (i.e., before swallow initiation, during the pharyngeal response, and/or post pharyngeal swallow). The timing of airway invasion informs clinicians of possible causative factors and allows for more tailored management strategies (26, 42, 66). Evidence based quantification of dysphagia symptom severity is possible with the Rosenbek 8-point penetration aspiration scale (PAS) (68), shown in Appendix 2. Detection of aspiration, particularly silent aspiration, is a key strength of VFSS. However, in severe cases when residue carries over from one bolus trial to the next and is not cleared from the airway, this can impact the accuracy of PAS scoring (65). VFSS provides important information about the oral phase of swallowing, particularly useful in children where oral skills are developing in relation to bolus containment, bolus formation, sucking rhythm, and the suck swallow breath pattern. On a case-by-case basis, with an experienced expert team, the VFSS assessment can be particularly useful to explore bolus flow rates, teat sizes, postural changes, texture changes, bolus placement, and other individualised therapeutic manoeuvres, which can enhance airway protection and efficacy of bolus clearance through the oral cavity and pharynx (67). Evidence of airway protection, bolus control, anatomic displacement and temporal measures of swallowing function and efficiency in bolus clearance are key benefits of the VFSS and provide valuable indication to guide therapeutic interventions.

Despite these key clinical benefits, the general limitations in clinical and research contexts of VFSS are well known and relate to the exposure of ionising radiation, the impact of the use of video x-ray frames per second, and limitation of the number of swallows acquired due to time constraints and radiation exposure (35). Additionally, the overall reports of poor intra- and inter-

rater reliability are discouraging (29, 69-71). Functional components of the VFSS provide the lowest rater reliability scores (72), and without rater training to study items, poor reliability has been demonstrated (73, 74). Specifically, airway invasion and residue have shown adequate reliability (72, 73). Regarding radiation exposure, experienced clinicians understandably use less fluoroscopy time than novice clinicians (75), and procedural protocols reduce fluoroscopy exposure time, although it has been shown that observed aspiration leads to the use of larger doses of radiation (76). Many clinicians defend the risk of radiation exposure as most children receive doses below the Australian Radiation Protection and Nuclear Safety Agency dose limit of 1 millisievert (mSv) per year for public exposure (77). Yet, temporal resolution is a key consideration for the accuracy of VFSS results. Rater accuracy of penetration/aspiration events has been studied for temporal resolution of 30 images/second and 15 images/second. Interestingly, with lower resolution, 20% of penetration/aspiration events were missed for raters who originally detected these events with higher resolution analysis (78). Overall, the factors of time constraints to minimise radiation exposure and assessor variability in the absence of automated analysis, inevitably contribute to the reports of poor intra- and inter-rater reliability of VFSS (36, 64, 79, 80).

Protocols in VFSS tend to be site specific, and standardised outcome measures of therapeutic effects and swallowing physiology are difficult to establish (29, 66, 69-71, 81, 82). For these reasons, VFSS as an outcome measure in research studies is often limited to establishing the presence or absence of aspiration or penetration (83-85). However, a recent paediatric study investigating swallowing outcomes after tracheoplasty also reported presence of delayed swallow trigger and epiglottic undercoating, which significantly enhanced reader appreciation of the clinical characteristics of this patient cohort. Nonetheless, in the absence of quantitative biomechanical measures, expert inference is needed to hypothesise the causes of the radiological observations made during VFSS (86).

There are ongoing efforts to enhance the diagnostic power of fluoroscopy, predominantly in the adult sphere. Standardised profiling has been defined, such as MBSImp™ (87), and has been

implemented in fluoroscopy research (88, 89). While MBSImp™ offers a standardised protocol with 17 quantifiable parameters, the time-consuming nature of taking these measurements may be the main reason for a lack of widespread clinical translation thus far. A standardised rating profile for infant VFSS assessments, the BabyVFSSImp© (90) has also been published recently. With 21 quantifiable parameters acquired per swallow, this rating profile will likely become a useful reference standard in clinical and research settings. Additionally, collaborators of these methods have attempted to create mathematically derived 'model parameters' to gain 'gradations of swallowing impairment' regarding pathophysiological contribution from the oral and pharyngeal phases (91). However, ongoing investigation and application of these complex calculations will be required to determine their clinical value. In contrast, semi-automated programs have been proposed by a range of research groups to radiologically track the trajectory of anatomical displacement and temporal measurements (92-95). These semi-automated methods include ImageJ software using the Analysis of Swallowing Physiology: Events, Kinematics and Timing (ASPEKT) method (96, 97), Swallowing Observer: Image & Physiology SL, Barcelona, Spain (98) and Swallowtail (Belldev Medical LLC, Arlington Heights, IL) (99). To our knowledge, Swallowtail software is the only VFSS automated analysis method applied in paediatric populations (81, 100, 101), and is one of the emerging methods to assist with overcoming the laborious manual extraction of quantitative fluoroscopy measurements. As VFSS is the most used and accessible instrumental dysphagia assessment, availability of automated software is promising for its ability to improve accuracy and reliability of VFSS analysis (101).

Until quantitative software analysis is applied more widely, the clinical interpretation of swallowing physiology (e.g., extent of laryngeal elevation or UOS relaxation) relies solely on rater judgement, with or without the assistance of standardised rating scales. Overall, intra- and inter-rater reliability may be improved with broader application of BabyVFSSImP™ and Swallowtail type analysis methods in the paediatric setting. The VFSS provides a snapshot of a person's swallowing function, therefore, particularly in children, patient cooperation during

the assessment can influence the quality and the total number of swallows acquired to generate a report. These factors are usually included in reports as they are important for result interpretation. For example, aspiration during crying or unsettled behaviour may not accurately represent a child's usual swallowing capability. Unfortunately, repeat VFSS assessments, including pre- and post- interventions, remain limited, especially in children as the risk of future malignancy related to radiation exposure is greater than in adults (71, 75, 77, 102).

Despite its limitations, the clinical confidence of VFSS affords its selection as the reference standard to test diagnostic accuracy of many other OPD assessments (69), even though there are limited reports of the diagnostic accuracy of VFSS itself. The only comparable reference standard is the Flexible Endoscopic Evaluation of Swallowing (FEES). A recent systematic review reported 'indeterminate' psychometric properties for both VFSS and FEES, as there is currently no single standardised protocol to evaluate image-guided analysis of swallow features (58); therefore, rater interpretation, expert or not, is subjective during VFSS and FEES. Broader application of BabyVFSSImp™ rating profile and Swallowtail software will likely improve the use of standardised protocols. When semi-automated analysis methods become more widely available for VFSS analysis, the reliability of radiological assessments will likely be significantly improved, and the enhanced objectivity will benefit research and clinical settings.

2.2.2 Flexible Endoscopic Examination of Swallowing

Flexible Endoscopic Evaluation of Swallowing uses trans-nasal flexible naso-endoscopy. Dysphagia assessment using FEES in adults was first applied in the late 1980s (103) and a decade later, FEES sensory testing (FEESST) was described whereby the scope is manoeuvred to touch the laryngopharyngeal mucosal walls in order to assess a patient's sensory function as a part of a dysphagia assessment (104). Sensory testing, secretion management and direct visualisation of anatomy are the key strengths of FEES (105), however, a 'whiteout' period occurs during the swallow response. Consequently, bolus movement before and after the swallow must be viewed in the chambers of the pharynx and larynx to infer swallow function efficiency. The procedure is presumably better tolerated in adults and older children compared to infants and young children, however the application of FEES for paediatric swallow assessments was first described in the mid-1990s (106). In some expert settings, FEES is a routine test used for evaluation of paediatric dysphagia (105). FEES has been shown to provide clear clinical value, particularly among neonates and breastfed infants as breastfeeding cannot be examined with VFSS (107-109). Sensory testing during FEES has also been applied in children, with a possible correlation seen for increased laryngopharyngeal sensory threshold in patients with GORD (110). Indications and contraindications of the FEES procedure have recently been summarised by Miller and Willging (105). They state that children can be proposed for FEES in the following contexts: if they are ready for oral trials; if oral secretion management needs further investigation; when structural abnormality of the pharynx or larynx is suspected or established, to ascertain impact on swallow function; if sensory threshold testing would be beneficial; to assess vocal fold mobility; and when radiation exposure is to be avoided i.e., when repeat measures are required in close succession. Contraindications include children with nasal obstruction or choanal atresia, children with stenosis of the pharynx, severe micrognathia (small lower jaw) and glossoptosis (tongue displacement towards the pharynx), and children with severe medical fragility (105).

The FEES procedure is predominantly performed by SPs who have typically undergone 10-14 hours of formal teaching in endoscopy skills and video interpretation, however in paediatric settings a nurse or otolaryngologist/ENT may also be present (111). Topical anaesthetic is commonly used to improve tolerance of the procedure but there is controversy of its impact on sensory function. Children undergoing endoscopic procedures benefit from topical anaesthesia (106) but this should be used with clinical discretion – children under 12 months of age, with severe neurological disorders, seizures and severe secretion management may be contraindicated for topical anaesthesia (105).

With or without anaesthetic, when the FEES procedure is carried out, pharyngeal and laryngeal anatomy is examined, and functional movement of the larynx and hypopharynx can be observed during phonation and respiration. These structures are also examined for symmetry, and mucosal appearance (107). A key benefit is assessment of secretion management prior to presentation of boluses, and with coloured food and liquid offered during the test, bolus movement pre and post swallow initiation can be visualised and distinguished from secretions (111). It is established that FEES is a safe procedure, when tolerated, often performed at the bedside or in the clinic setting (112). The advantages of FEES over VFSS include the ability to directly visualise pharyngeal and laryngeal structures, without the risk of ionising radiation exposure. Evaluation of laryngeal structures is clearer with FEES and although it is less widely utilised, FEES is particularly valuable in children with suspected laryngeal anomalies. The main limitation of FEES relates to the ‘white out’ period during the pharyngeal contraction, which may lead to missed diagnosis of micro aspiration events (113) and reports of quantifiable or quantitative FEES measurements are lacking in the literature (114).

Comparative studies using VFSS and FEES are difficult to perform due to technological complexities and the test burden required of patients. Therefore, the FEES literature is especially limited in children. A few studies have considered the agreement of parameters measured on VFSS and FEES in children. One such study compared VFSS and FEES in infants, mean age 25 months, and showed low diagnostic agreement (115). In this study, FEES

proved to have a higher specificity and positive predictive value of laryngeal penetration/aspiration compared to that seen on VFSS despite a lack of standardised FEES evaluation items. Another study found 100% agreement for blinded aspiration and penetration ratings, notably achieved by two highly expert investigators (116). Beyond the evidence of pre- and post- swallow airway protective mechanisms and penetration and aspiration status, objectifying measures of swallowing physiology is difficult to achieve with FEES, the assessment is particularly subjective and it has been recommended that validated measures are required to improve the FEES assessment (114).

Overall, there is good evidence to support the clinical performance of FEES in paediatrics as shown by expert application of the technique, with over 7000 paediatric procedures performed in one particular centre of excellence in the USA (105). However, application of FEES has not been achieved in paediatric settings to this extent within Australia, and the development of validated FEES measures are required.

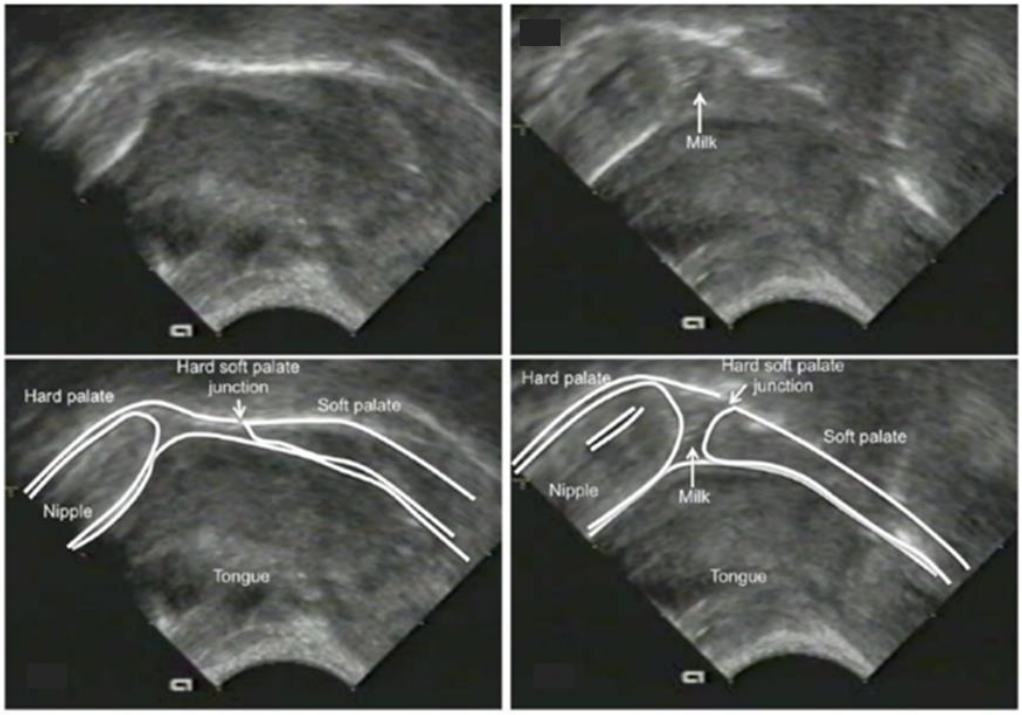
2.2.3 Ultrasound

In the medical setting, ultrasound is an imaging tool that employs a transducer held against the body part being examined to receive sound waves of vibrational energy occurring at the interface between somatic tissues. These signals are decoded and transformed into images which are displayed on a computer screen for visual analysis (117). Due to its non-invasive nature, ultrasound has been explored for use in swallowing assessments and previous literature predominantly details its application in conditions of the oesophagus, such as GORD and to track bolus presence and estimate pathology in the cervical oesophagus(118-121). It has also been used to determine the impact of motility disorders such as achalasia, diffuse spasm, and hypercontractility of oesophageal circular and longitudinal muscles (122). Recent application of 3D ultrasound in the oesophagus has demonstrated the ability to detect oesophageal atresia in utero, which has significant implications for improvements in prenatal counselling for parents and perinatal management for infants with this diagnosis (123).

Advances in the resolution of ultrasound images over the past decade have enabled improved detail of infant sucking assessment (18, 124-126). Parameters measured with ultrasound include the distance between the breast nipple and the infant's hard palate (mm); depth of the infant's intraoral space (mm); nipple diameter (mm); and mid-tongue depth (18, 124-126), as displayed in Figure 2.2. The relationship between these measurements, e.g. nipple diameter and intraoral space, can be correlated to determine infant sucking efficiency (18). Imaging can be acquired in a range of planes (sagittal, transverse, or axial) to orientate and describe the sucking mechanism. In this context, the technique is reportedly enhanced when combined with intraoral vacuum measurements, which together provide indication of suction effectiveness i.e., a stronger intraoral vacuum is associated with more effective feeding (18). This may be particularly useful in children with oral anomalies such as cleft palate, or in children expected to have reduced suck strength as shown in infants with Trisomy 21 (127). Other ultrasound studies in preterm and newborn infants show that tongue movements mature rapidly with nutritive sucking, and the nutritive sucking action (compared to non-nutritive sucking) is

characterised with greater mid-tongue movements (126). A study of the lingual surface patterns observed in pre-term infants showed wave-like lingual patterns representative of what is expected for infants 6-9 months neuromaturational age, suggesting that ultrasound may advance what is known of oral stage swallowing, particularly in developing infants (128).

Figure 2.2. ***Ultrasound images of breastfeeding***



Note. This figure demonstrates ultrasound images of infant breastfeeding; the bottom panels provide labels to aid familiarity. Image reprinted from *Geddes DT, Sakalidis VS. Ultrasound imaging of breastfeeding - A window to the inside: methodology, normal appearances, and application. J Hum Lact. 2016;32(2):340-9, reproduced with permission.*

In the hands of experts, ultrasound has also been used to establish the pharyngoglottal closure reflex in infants, whereby glottal adduction frequency, response time and duration of closure were shown to be the most prompt reflexes that occur with spontaneous sucking, compared to provoked pharyngeal swallowing (129).

Other aspects of pharyngeal swallowing have been reported with ultrasound, relating to hyoid and laryngeal movements (130-132) and bolus transit through the pharyngeal area has also

been reported (125). Capturing swallowing function according to the rhythm and extent of hyoid movements, in combination with the ability to determine milk flow, has clinical value for the assessment of breastfeeding infants experiencing feeding difficulties. As this non-invasive test can be performed in a clinic setting, it may provide specific value for infants requiring repeat evaluation during the weeks of establishing lactation. Additionally, a recent study reported the hyoid bone is unreliably visualised with VFSS in infants < 9 months of age (133), therefore the application of ultrasound may provide an alternative for assessing extent of hyoid movements in children under 9 months of age. The application of ultrasound has also been shown in healthy pre-school children where hyoid bone movements were successfully determined, with displacement of 0.3 cm in 99% of the swallows analysed (131). Healthy reference ranges in paediatrics are rare to find, however will greatly benefit the interpretation of ultrasound examination in children with OPD. A separate study of a cohort of children with cerebral palsy (CP) (median age three and a half years) showed hyoid and laryngeal movements were evidently reduced in the presence of symptoms of pharyngeal dysphagia shown on FEES (132).

Evaluating swallowing physiology with ultrasound is limited to the isolated swallowing feature being imaged i.e., hyoid bone or laryngeal displacement, or milk flow through the pharynx. Overall, the utility of ultrasound for OPD assessment appears most promising for preterm and young infants, because ionising radiology can be avoided, offering a unique investigation of specific aspects of breastfeeding. Evaluating the pharyngoglottal closure reflex provides information regarding an infant's ability to protect the airway, which holds value for assessing vulnerable infants at risk of aspiration, to determine a baby's vigilance in airway protection and may assist in determining readiness for oral feeding (129). However, the technique does not offer a dynamic assessment across all phases of swallowing, requires expertise in transducer positioning and orientation and visual interpretation of the somewhat abstract images is subjective and reliant on extensive experience. Further investigation into the intra- and inter-rater reliability will be required to determine ultrasound accuracy and its future clinical value.

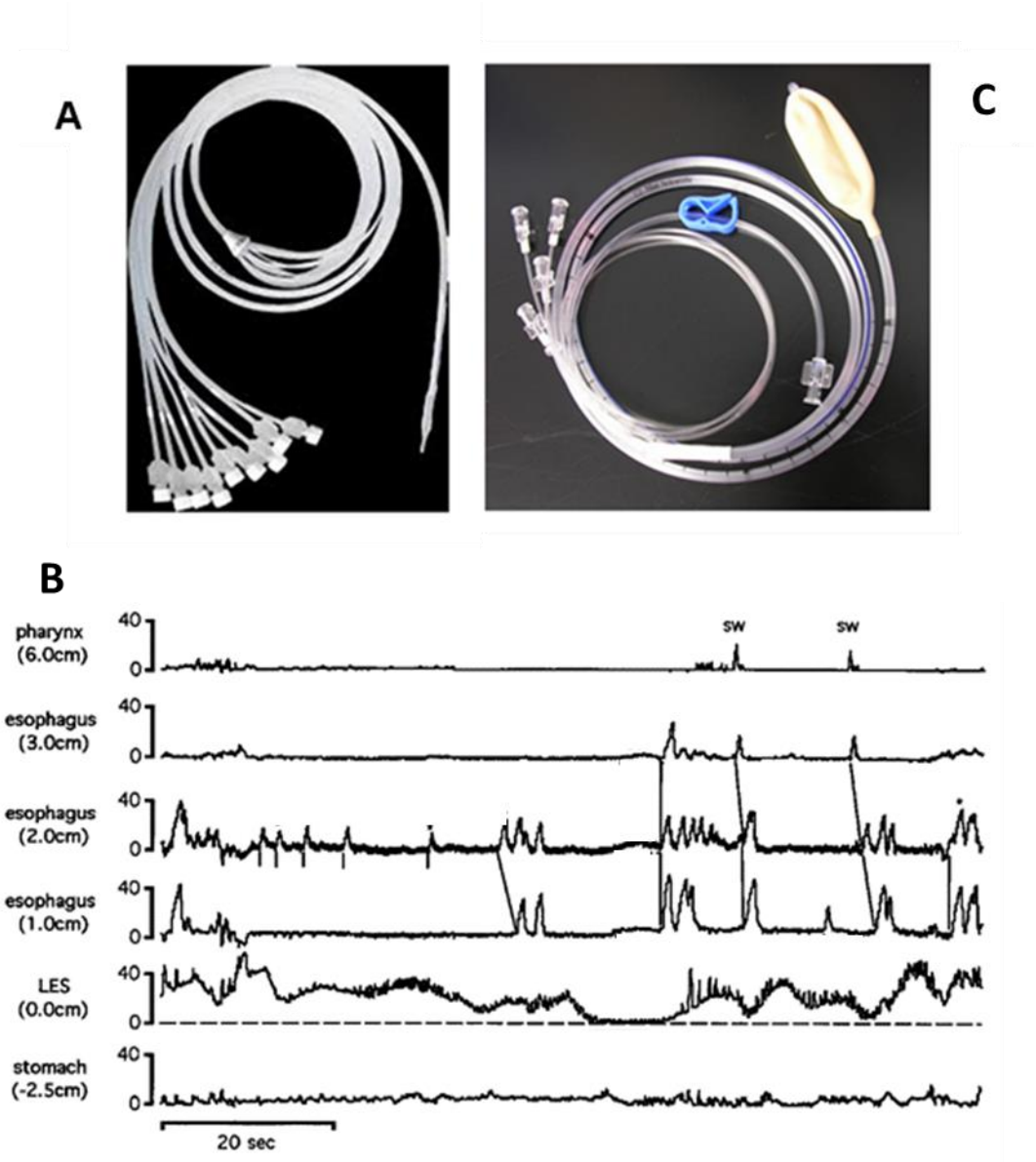
In summary, each visuo-perceptual assessment tool provides unique and important contributions to the overall evaluation of paediatric OPD. While these methods predominantly rely on interpretation of image data, more quantitative approaches are emerging. Currently, VFSS remains the most widely implemented instrumental assessment tool, with increasing use quantifiable rating scales and promising semi-automated quantitative analysis methods (81, 90, 100, 101). The FEES procedure provides unique evaluation of secretion management, direct visualisation of the anatomical structures of the pharynx and larynx and enables sensory testing, however, is lacking in quantifiable measurements to date. Ultrasound is a non-invasive, clinic-based assessment tool which is showing unique potential for the evaluation of infant sucking. It mainly relies on qualitative evaluation of image data, although there is evidence of computerised analysis of tongue surface movements (134). With all three instrumental assessment tools, standardised protocols enhance the interpretation of the image data.

The following section outlines, manometry as a complementary technique to the assessment tools presented above. The complex pressure changes that occur throughout the pharynx and UOS during swallowing can be recorded with manometry techniques, and manometry with impedance enables the interactions between swallowing pressures and bolus flow to be derived. To contextualise P-HRM-I as the index test used in this thesis, a brief history from conventional, low-resolution manometry to currently utilised high-resolution methods is included in the section below.

2.2.4 Manometry

Manometry has been used to evaluate swallowing physiology for over 50 years and has seen a range of technological advances, particularly in the past decade (59). Manometry refers to the measurement of pressure. As the swallowing mechanism is a pressure driven event, it is not surprising that manometry was explored as early as the 1950s for assessment of swallowing physiology (135). Originally, manometry was developed as a catheter-based test to measure intraluminal pressure in the oesophagus and other parts of the gastrointestinal (GI) tract to indicate motility events. Conventional manometry methods relied on pressure detection with volume displacement transducers using water perfused technology, which converted pressure signals into waveform tracings; see Figure 2.3, panel B (135). In its most rudimentary form, manometry involved low-resolution single sensors, which generated pressure waves at single locations along the oesophageal or upper sphincter regions. Acquiring meaningful assessments particularly through sphincter regions was problematic. Specifically, the rapid contractile responses of the pharyngeal and UOS region were difficult to record accurately due to the discordant movement of the UOS with the manometry catheter, and the need to detect the rapid responses and pressure changes in this region (136). The e-sleeve (Dent sleeve) developed in 1976 enhanced manometry investigation because it enabled a more dynamic assessment of the rapidly occurring deglutitive pressure events, in particular overcoming the challenge of measuring sphincter movement (137); see Figure 2.3, panel C. For its time, this was a true advance in the assessment of sphincteric relaxation pressures. While conventional manometry was used for oesophageal studies for over 30 years, the luminal asymmetry of the pharynx and UOS posed further issues for accurate pressure detection. In addition, the continuous ‘drip effect’ during water perfusion was an aspiration risk in severely dysphagic patients (138, 139). In healthy individuals with intact pharyngeal sensation, the drip effect led to isolated pharyngeal swallows triggered by the water perfused directly to this region, which created an additional interference in the pressure recordings (140).

Figure 2.3. ***Conventional water perfused manometry catheters***



Note. This figure demonstrates in Panel A: a conventional water perfused manometry catheter (obtained from the public domain); Panel B: low-resolution pressure waveform tracings of the pharynx and oesophagus (sw=swallow), image obtained from *Omari TI, Benninga MA, Barnett CP, Haslam RR, Davidson GP, Dent J. Characterization of esophageal body and lower esophageal sphincter motor function in the very premature neonate. J Pediatr. 1999;135(4):517-21, reproduced with permission;* and Panel C: Dent sleeve for pressure acquisition across upper oesophageal/lower oesophageal sphincter.

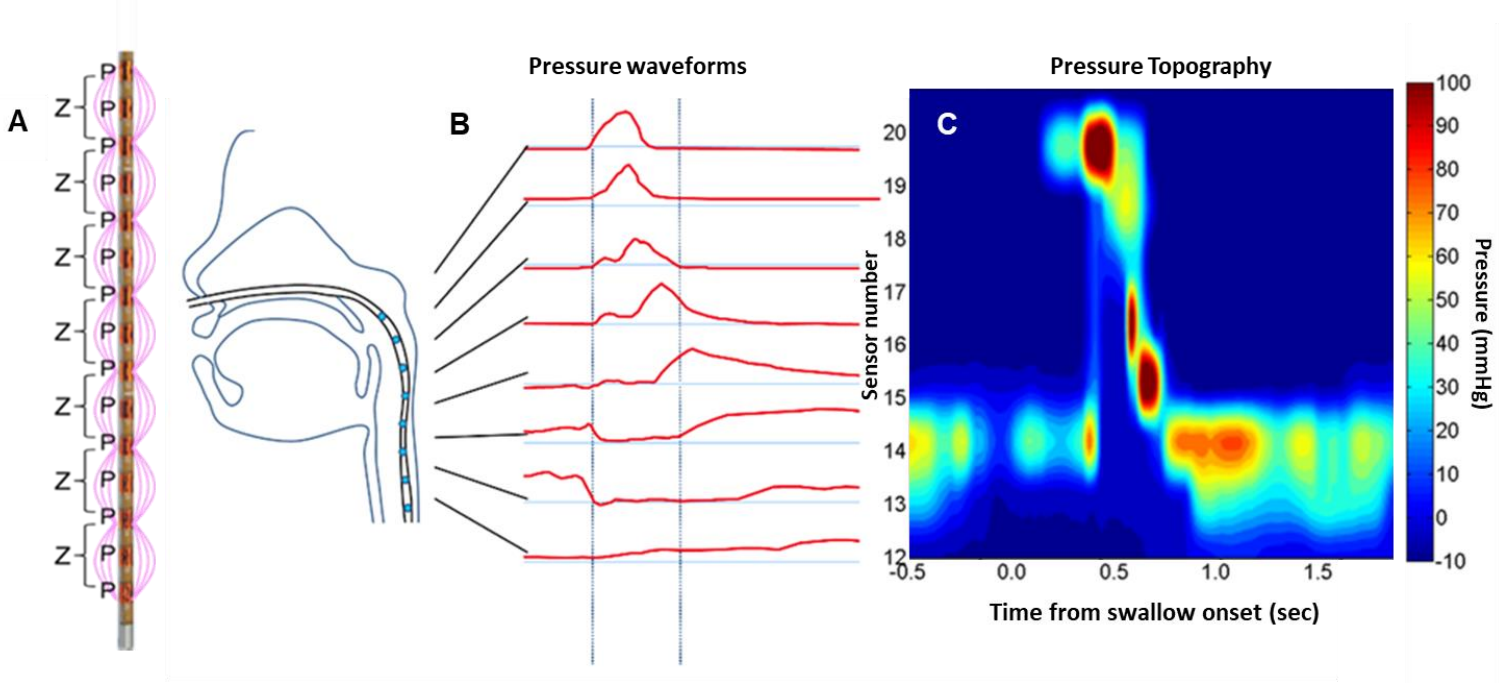
Noting these limitations of conventional water perfused manometry methods is important to appreciate the technological advances in manometry methods over the past two decades. The

section below outlines the use of solid-state sensors in manometry catheters and how this development improved the application of manometry in swallowing assessments.

2.2.5 High Resolution Manometry

To overcome the challenges of conventional manometry, several key technological advances over the past two decades brought about high-resolution manometry (HRM). Multi-channel HRM catheters incorporate solid state pressure sensors spaced 1cm apart along the catheter, allowing for continuous interpolated pressure recordings across all segments of the swallowing mechanism (141-143); see Figure 2.4, panel A. Additionally, the movement away from water perfused towards solid state sensors improved the reliability of recording rapid, continuous movements throughout the swallowing mechanism, including the pharynx (144). As a result, HRM is increasingly being studied for its use in OPD (136, 138, 145-149). The benefits of HRM are particularly evident in the pharyngeal phase of swallowing, where the intricate pressure variations and temporal measures at the velopharynx, tongue base, and upper sphincter zones can be recorded simultaneously (70, 150-156). The display and analysis of HRM data has also advanced from conventional line wave forms to pressure topography or Clouse plots, which depict sensor position and pressure values, coded by colour intensity; see Figure 2.4 panel B and panel C. Pressure topography is a vast improvement on the line wave forms used in conventional manometry as it enables easier and more accurate placement of the catheter assembly (157) and provides assessor guidance of overt swallowing features, such as UOS hypercontractility. The swallowing physiology captured by HRM is outlined in Section 2.3.1.

Figure 2.4. ***Schematic of high-resolution manometry pressure waveforms and topography***



Note. Panel A: schematic of a high-resolution manometry catheter with pressure sensors spaced 1cm apart (P=pressure sensors, Z=impedance electrodes). Panel B: schematic of HRM manometry catheter in situ, with depicted pressure waveforms. Panel C: colour topography plot.

2.2.5.1 Unidirectional and Circumferential Pressure Sensors[3]

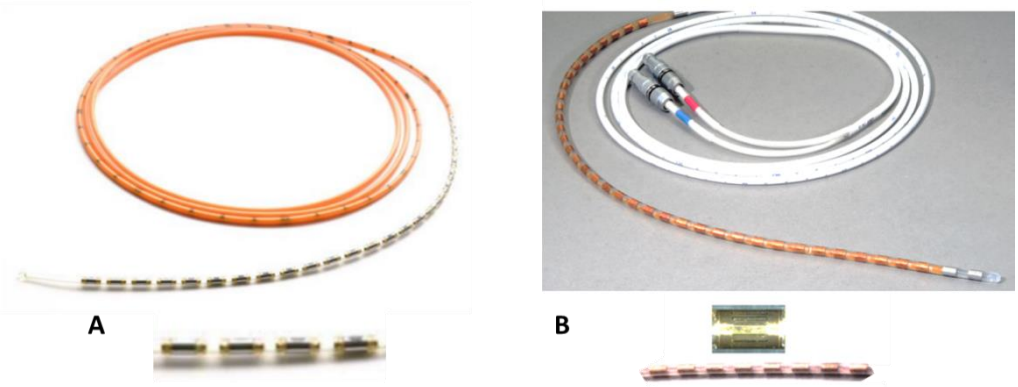
Individual catheter specifications relating to directionality of sensor arrays must be discussed for their influence over pharyngeal pressure results (158-161). This particularly relates to the luminal asymmetry of the pharyngeal and UOS regions, an issue that must be considered during manometric pressure assessments. Figure 2.5 shows examples of unidirectional (panel A) and circumferential sensor (panel B) catheters. Each has advantages and disadvantages for use in OPD, particularly when considering application in children. The irregular shape of the pharynx in combination with the use of unidirectional pressure sensors may impair reliability of pressure measurements, particularly within the mesopharynx and hypopharynx where

[3]This text has been developed and extended from a section of Chapter 4, previously published as: 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. 2017; 128(6):1328-34.

asymmetry is most pronounced. Indeed, studies investigating the symmetry of deglutitive pharyngeal and UOS pressures using state-of-the-art 3D circumferential HRM catheters have recently highlighted the asymmetrical pressure generation in the pharynx during swallowing, with substantial variation seen at the base of tongue and hypopharyngeal regions (158-161). The use of circumferential 3D investigation has also shown the impact of posterior pharyngeal pressures on overall pharyngeal contractility, whereby the posterior orientation of muscle fibres, the presence of hard spinal structures and the anterior laryngeal movement all contribute to the variation of pharyngeal measures (159). It could be argued that circumferential sensors are, therefore, optimal for pharyngeal manometry. However, this may be an oversimplification, as existing circumferential sensor technologies also have limitations. For example, standard large array circumferential sensor devices currently in routine use, only provide circumferentially *averaged* results for each sensor, which is not necessarily akin to obtaining multiple separate, radially orientated readings (159). Furthermore, parameters of pharyngeal peristalsis, even when based on circumferentially averaged pressure measurements, have shown significant intra- and inter-subject variability (162). Additionally, research conducted using parameters developed by our research group, also based on circumferentially averaged pressure measurements, showed poor test-retest reproducibility, particularly for pharyngeal contractility measurements (163). In contrast, hypopharyngeal intra-bolus pressure (IBP) and flow timing measures were far more reliable (163). Hypopharyngeal IBP, whilst measured at a region of pronounced pharyngeal asymmetry, generates a highly symmetrical reading with circumferential measurement, likely due to the equalised pressures within the bolus space at this time point in the swallowing process (159). This provides some support for the credibility of obtaining unidirectional measurement within the asymmetrical pharyngeal chamber, which is potentially less influential over the overall pharyngeal pressure recordings in paediatric patients who have smaller anatomical structures and pharyngeal spaces. However, technological advances have seen circumferential catheters reduce to as low as 2.75mm in diameter, although this is for HRM-only catheters without integrated impedance electrodes (Manoscan™). Catheters that include both pressure sensors and impedance electrodes are

available at 4.2mm outer diameter from Manoscan (MSC-3890-Z), and a combined unidirectional and circumferential sensor catheter with 31 unidirectional pressure sensors and 5 circumferential sensors for lower oesophageal sphincter assessment is available at 3.2 mm outer diameter from MMS, Laborie (K103659-E-1545-D).

Figure 2.5. ***Unidirectional and circumferential catheters***



Note. Panel A shows a 3.2mm unidirectional HRM-I catheter; Panel B shows an example of a 4.2mm circumferential HRM-I solid state pressure and impedance catheter incorporating 36 1 cm-spaced pressure sensors and 18 adjoining impedance segments, each of 2 cm length (Given Imaging, Ltd.)

In summary, with regards to the developments of manometry techniques for acquisition of deglutitive measures over the past two decades, technological advancements have led to high resolution manometry recordings and pressure topography depictions of swallowing, which guide catheter positioning and timing of swallowing acquisition with greater accuracy; and we see that directionality of the manometry sensors (unidirectional vs. circumferential) influences the type of data acquired, each with pros and cons and contexts for which they are best utilised.

The most recent development, integrated HRM with impedance (HRM-I), has predominantly been available as unidirectional pressure sensor catheters, and up until now has been applied in children, as these catheters had a narrower diameter, and a flatter, more comfortable surface. Additionally, the impact from pharyngeal asymmetry is expected to be less of an issue

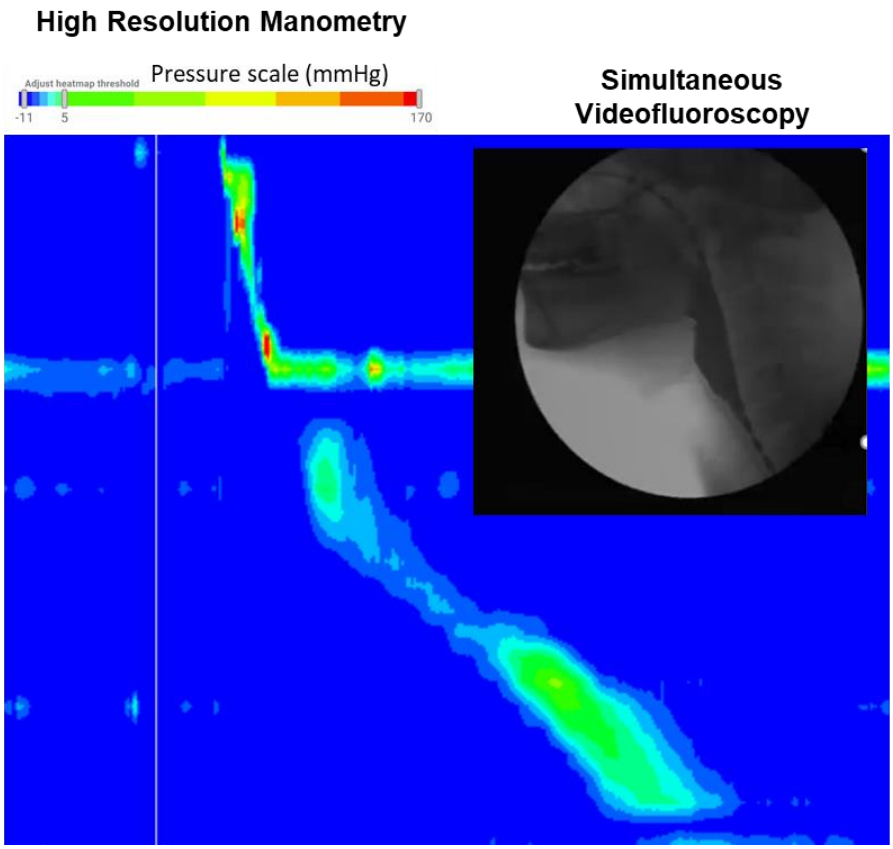
in paediatric participants who exhibit smaller pharyngeal and UOS chambers. Future studies should formally test the impact of manometry sensor directionality as circumferential catheters are now available in small French (diameter) size. Ultimately, the value of HRM recordings is most apparent for its ability to provide quantitative indications of swallowing biomechanics, which can be used as outcome measures for correlation with clinical dysphagia symptoms and therapeutic interventions. The specifics of HRM parameters will be outlined in Section 2.4. HRM is becoming more widely recognised for its ability to improve diagnostic accuracy, particularly when unusual bolus flow movements cannot be explained from visuo-perceptual assessment alone (155).

It is important to note that pressure recordings are most meaningful in the context of bolus flow dynamics and the following sections outline the advantages of integrating fluoroscopy (Section 2.2.6) and impedance (Section 2.2.7) with manometry as options to achieve this.

2.2.6 Videomanometry

Videomanometry, or manofluorography, refers to the concurrent use of manometry and fluoroscopy/fluorography to assess OPD; see Figure 2.6. Videomanometry has been used to analyse normal and disordered swallowing across the lifespan (140, 164-170). The benefit of the combined techniques is the capacity to visualise movements of swallowing structures and bolus flow (including evidence of penetration/aspiration and residue), whilst simultaneously detecting objective pressure parameters in the pharynx and UOS.

Figure 2.6. ***Videomanometry***



Note. Example of a 20ml liquid bolus captured in a healthy participant.

Videomanometry led to the first reports of bolus flow resistance through the pharynx in different patient groups (140, 165, 166, 168, 171), and the first reports of the UOS intra-bolus pressure (IBP) parameter as investigated with failed UOS opening in patients with OPD (172, 173). The IBP is a measure that has clinical application not achievable with VFSS or manometry alone

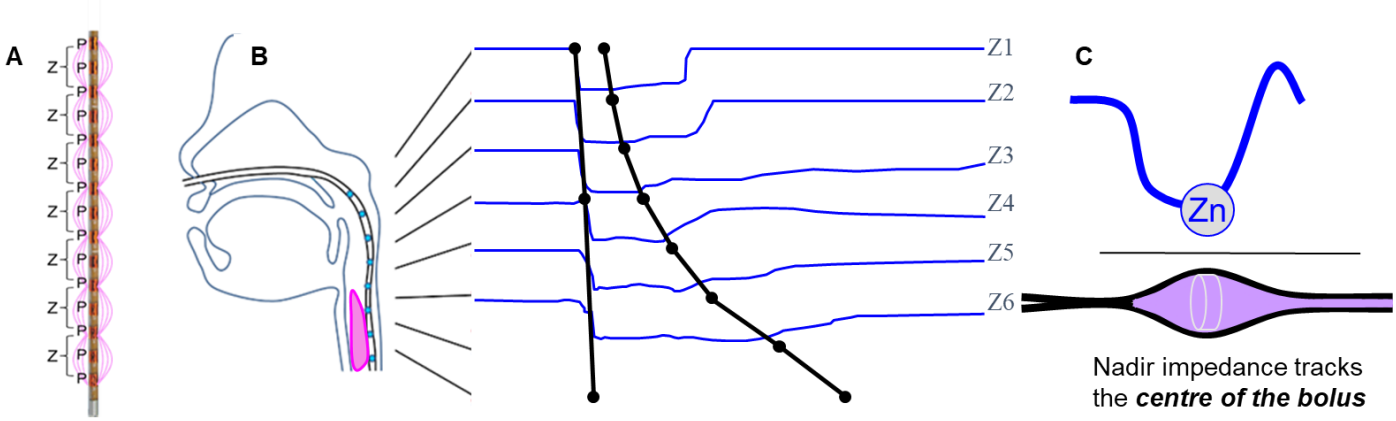
and has specifically shown its worth as a diagnostic tool and outcome measure post intervention for patients with UOS restriction in the case of hypercontracted cricopharyngeal bar (61). With the use of more accurate diagnostic methods to describe pathophysiology, clinical decision making is improved. The benefit of videomanometry has recently been shown in a cohort of patients with multiple system atrophy, where elevated UOS resting pressures were detected as an early sign of OPD (171). The early detection of OPD pathophysiology as shown in this study, will optimise the implementation of measures required to ensure swallowing safety in all patients with degenerative neurological conditions, who are especially vulnerable to aspiration related pulmonary disease.

Overall, videomanometry allows the identification of measurable pressure dynamics in the context of visualised bolus flow seen on VFSS. This multi-modal approach to swallowing assessment is comprehensive and enhances the evaluation of underlying pathophysiology and subsequently, the clinical decision making for patient management (140). There are logistical challenges associated with employing these two complex methodologies simultaneously. Challenges relate to synchronising the technologies, recording useable recordings influenced by patient tolerance (which is particularly challenging in the paediatric setting), as well as the time and expertise taken to separately analyse and interpret the radiological and manometric recordings. Fluoroscopy is exceptional for its clinical value in determining the degree of airway invasion and extent of swallowing musculature movements (in the oral and pharyngeal phases of swallowing). However, in the setting where fluoroscopy and manometry protocols are either too cumbersome to perform simultaneously or too onerous for the patient, stand-alone P-HRM-I may be considered. P-HRM-I is a single catheter assessment which generates integrated pressure and bolus flow dynamics through the pharynx and oesophagus and is discussed below.

2.2.7 Pharyngeal High-Resolution Manometry with Impedance

Impedance was first applied in the mid-1990s in GORD patients for the investigation of oesophageal flow dynamics (174, 175) and combined with pH monitoring, continues to be used to evaluate GOR (176-178) and rumination syndrome (179) in children. A solid-state HRM-I catheter combines manometry sensors (spaced 1cm apart for high resolution) and impedance electrodes (at 2cm intervals); see Figure 2.7 panel A. With integrated impedance electrodes a constant electrical current is generated between the evenly spaced impedance electrode pairs, each of which is referred to as one impedance segment (180). Impedance recordings are based on the catheter's ability to detect surrounding matter, which may increase or decrease the resistance to the alternating electrical current passing between impedance segment electrodes (180). For example, air boluses are less conductive and thus produce a higher impedance reading compared to liquid boluses, which produce lower impedance readings. Importantly, impedance measurement is affected by the conductive properties of a bolus (181, 182). Figure 2.7 panel B and C show the drop in impedance (measured in Ohms) during passage of a conductive, luminally distending bolus (bolus conductivity is discussed below). The nadir impedance value tracks the axial centre of the bolus; see Figure 2.7 panel B and C.

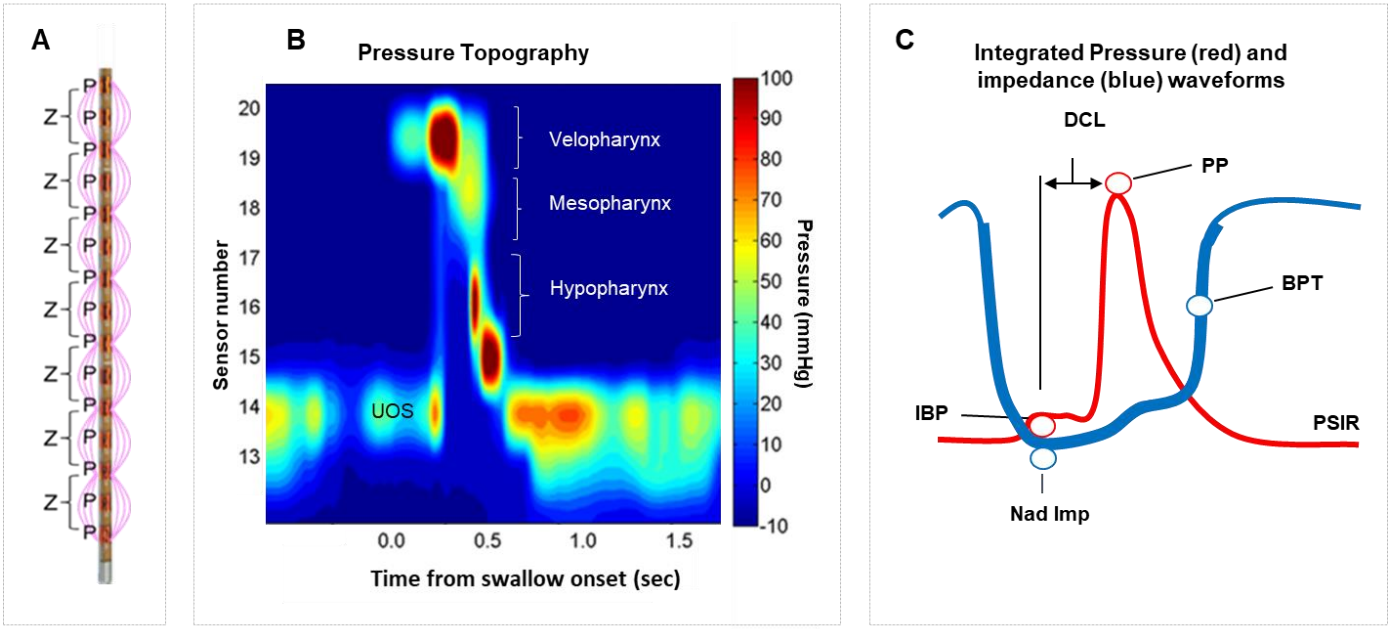
Figure 2.7. ***Schematic of impedance waveforms***



Note. Panel A: Schematic of HRM-I catheter, Z denotes impedance segments 2cm apart, P denotes pressure sensors 1 cm apart. Panel B: Schematic of catheter in situ, Z shows impedance and each blue line depicts the drop in electrical resistance as the bolus passes each impedance electrode segment. Panel C: Nadir impedance (Zn) which tracks the axial centre of the bolus. Note, HRM recordings (as was shown in Figure 2.4) occur simultaneously during P-HRM-I studies.

Swallow signatures displayed on topography plots, signify contractility (lumen occlusion) of the swallowing musculature in space and time and impedance data are embedded; see Figure 2.8 panel B (157). During recordings, manometry and impedance data are generated continuously, leading to vast amounts of swallowing data. These pressure topography plots guide and define the important pressure and impedance measurements at different time points of the swallow, providing a dynamic and objective assessment of swallowing pressures and the associated bolus flow patterns. Integrating the impedance and HRM waveforms provides detailed spatiotemporal measurements and swallowing motility can be interpreted more accurately in the context of bolus flow dynamics; see Figure 2.8 panel C (175). The pharyngeal swallowing physiology captured by P-HRM-I is outlined in Section 2.3.1.

Figure 2.8. ***Integrated pressure and impedance waveforms***



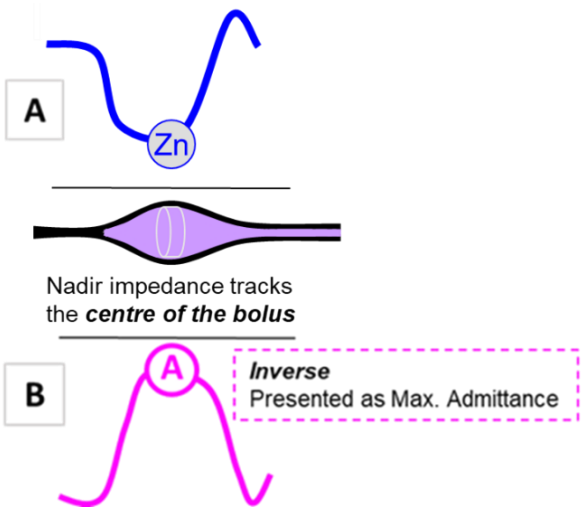
Note. This figure demonstrates: in panel A schematic representation of the HRM-I catheter; in panel B the pressure topography (reds high pressures, blues low pressure) with embedded impedance (not visible); and panel C the integrated pressure and impedance waveforms occurring during pharyngeal swallowing. Interactions between waveform data generate P-HRM-I pressure flow parameters. A select set of pressure flow parameters are demonstrated in panel C. Abbreviations represent the following metrics: DCL=distension contraction latency, PP=peak pressure, BPT=bolus presence time, PSIR=post swallow impedance ratio, Nad Imp=nadir impedance, IBP=intra-bolus pressure. The abbreviated pressure flow parameters will be described in further detail in the overview of methods, in Chapter 4.

As the manometry and impedance technologies are combined in a single catheter, this overcomes many of the logistical challenges of videomanometry. However, accessibility to these technologies, patient presentation, and medical team expertise will determine which combined methods (videomanometry and/or P-HRM-I) are employed in OPD assessments. Each of these instrumental assessments requires specific bolus preparation to optimise reliability of bolus detection. Like the need for contrast substances with fluoroscopy, P-HRM-I requires optimised bolus conductivity for electrical registration across the catheter electrodes. Further information regarding bolus conductivity is outlined below.

2.2.7.1 Bolus Conductivity and the Impedance Inverse: Admittance

Boluses offered during P-HRM-I studies require optimally conductive properties to be registered by the impedance electrodes within the HRM-I catheter (180). The impedance method works optimally when the electrical conductivity of the bolus is greater than that of the surrounding tissue (180). Substances with more free ions improve electrical conductivity, as is the case with sodium chloride solution (0.9% NaCl), also referred to as standard saline. Therefore, many original impedance swallowing studies of the pharynx (54, 183, 184) or oesophagus (178, 185, 186) used standard saline (0.9%) as a thin fluid bolus medium. The impedance signal can also be converted to its inverse product, milli Siemens *admittance* (i.e., mS = 1/Ohms), which has the advantage of exhibiting a linear relationship to luminal area; see Figure 2.9.

Figure 2.9. ***The Inverse of Impedance: Admittance***



Note. Panel A shows nadir impedance (Zn) which tracks the axial centre of the bolus. Panel B shows inverse of impedance presented as Maximum Admittance.

In summary, it is well established that HRM and HRM-I techniques are promising research tools and have great potential value in the clinical setting (70, 155, 187-193). The clinical translation and utility of manometry methods depend on the usefulness of the vast amounts of data acquired in a continuous fashion across a range of locations and time points during a swallowing assessment and the accessibility of the results and the way they are presented and

interpreted is important (194). Therefore, efficient interpretation methods and algorithm-based analysis is necessary to expediate and automate the extraction relevant swallowing information for clinical diagnosis and ongoing management of patients. An overview of automated manometry analysis methods is provided below.

2.2.8 Interpretation Methods for HRM and HRM-I

The description of pharyngeal and UOS swallowing biomechanics with manometry metrics is not a new endeavour although the majority of previous research has focussed on manual analysis of pressure-only measurements (59, 145, 150, 151, 167, 195-198). Manual extraction of clinically salient information from pressure (and admittance) curves is laborious and, in some cases, may amount to an overly simplistic analysis. Automated systems are required to improve the efficiency of analysis from the large volume of data generated per swallow. Swallowing parameters generated by computer-based algorithms, accelerate analysis and interpretation time, in turn, facilitating the likelihood of translating HRM and P-HRM-I into widespread clinical practice (194). Comparison of manual analysis and MATLAB (Mathworks Corporation) based algorithm analysis of a range of pharyngeal parameters showed strong correlations between manual and semi-automated results, demonstrating the reliability of automated analysis, which was suggested to improve overall efficiency of the analysis process (194).

Many research groups utilise semi-automated, algorithm-based analysis approaches that are available with commercial software such as ManoView™(147, 167, 192) or Bioview® (149, 199, 200). These packages were developed predominantly for analysis of oesophageal motility. As such, adjustments to pre-set regions of interest, typically programmed to the oesophagus, are required to generate pharyngeal pressure measurements, e.g. the pharyngeal pressure integral (147). Such efforts reflect a growing interest to investigate and report the pharyngeal swallow with novel parameters. However, adjusted oesophageal metrics are non-specific, and

sub-optimal for the measurement of the complex dynamics of pharyngeal contractility. Therefore, implementation of purpose designed software, which enables customised contractility, distension and bolus flow timing measurements of the pharyngeal and UOS zones, is likely to provide a superior approach. To enhance the relevance of HRM studies, it is now recognised that manometry findings are best interpreted in the context of bolus flow patterns (178, 181, 182, 190, 191, 201-208). The extent of impedance/admittance data integration within commercially available software packages varies, as does the level of expertise required for analysis.

Across the recent literature there is a growing interest in applying algorithm-based analysis to semi-automate evaluation of both radiological (81, 90, 98) and HRM and P-HRM-I swallowing analysis methods (147, 194, 209-211). Quantifying measurements with semi-automated software helps to standardise calibration and analysis processes, shortens analysis time (212) and, with robust intra- and inter-rater reliability (213-215), this is likely to produce more comparable measurements against normative reference ranges, between patients and within patients when tracked over time.

The HRM-I analytical methods currently implemented in our research group occur via the purpose-designed Swallow Gateway™ online portal (see Chapter 4: Overview of Methods). Purpose designed semi-automated analysis utilised in this research program was developed to extract specific measurements of interest. Other research groups have applied similar software for the measurement of pharyngeal pressure events, partially to expedite the analysis processes and to enable customised measurements of interest (194, 209-211). An example is the customised derivation of unique rostral UOS pressure patterns using a circumferential catheter combined with cricopharyngeal EMG and VFSS to confirm UOS relaxation and opening (216). Customised MATLAB programs enabled this analysis and authors reiterate the need for closely spaced sensors for analysis of the UOS (216). While fine needle EMG has been applied in adult populations to provide objective data on contractions and relaxations of the cricopharyngeal and suprahyoid muscles (199, 217, 218), this technique is invasive and

requires participant cooperation to remain steady through the investigation, therefore is not appropriate for application in children.

In summary thus far, VFSS is widely used as the reference standard in instrumental paediatric dysphagia assessment (64), FEES is employed in some settings (105), and ultrasound is emerging as an effective assessment tool for infant breastfeeding (18, 126, 128). All three visuo-perceptual investigations offer a unique and dynamic assessment of the integrity of swallowing structures, their movements and extent of airway protection mechanisms. The utility of HRM methods is increasing in research and clinical contexts as a quantitative, non-radiological technique that provides swallowing pressure and impedance profiles of swallowing physiology and for biomechanical interpretation of the clinical symptoms of dysphagia. Recognising that no single test provides complete assessment of the functions that ensure safe and effective swallowing, the exploration of new assessment techniques, which potentially add to the diagnostic detail of OPD is warranted. Additionally, the use of HRM methods in paediatric centres is increasing, with five known Australian tertiary healthcare institutions now implementing HRM or HRM-I techniques for oesophageal and in some cases pharyngeal assessment. Advances in HRM technology and the accessibility of purpose designed semi-automated analysis software enhances result reliability and improves diagnostic potential and practical application in the clinical setting. To provide context for manometry use in the paediatric setting over the past two decades, the following section outlines the main research studies, patient groups, technologies, and parameters employed in the evaluation of dysphagia in children.

2.3 Overview of Manometry Use in Paediatric Dysphagia Assessment since 1998

To provide context for the investigation of manometry in paediatric swallowing assessments over the past two decades, Appendix 6 details the main studies (low-resolution and HRM) conducted over the past two decades. The manometry protocols, analytic techniques, swallowing parameters measured, and findings of each study (pharyngeal and oesophageal) are included. The table in Appendix 6 demonstrates that across this time period, the paediatric manometry literature focused predominantly on the application of low-resolution methods to describe oesophageal motility in infant reflux disease and achalasia, and to describe the developmental oesophageal characteristics in infants. Additionally, aerodigestive reflexes have been comprehensively investigated and described by Jadcherla and colleagues, who, until recently, also utilised low-resolution conventional manometry methods. This group has significantly contributed to the paediatric literature showing that aerodigestive reflexes initiate in a dose-response fashion, by pharyngeal and oesophageal mechanical and chemical provocations (219, 220). With integrated manometry, respiratory inductance plethysmography and a nasal airflow thermistor, these authors have also described deglutition apnoea duration, which is demonstrated to decrease with healthy infant maturation (221). It is proposed that prolonged deglutition apnoea and/or altered pharyngeal reflex responses is suggestive of brainstem dysregulation, such as in the case with neonates experiencing apparent life-threatening events (222). Whether P-HRM-I can add to this knowledge of aerodigestive reflexes remains to be determined, however recent application of HRM-I in the oesophagus of preterm infants has revealed elevated flow resistance at the level of the oesophago-gastric junction in babies with bronchopulmonary dysplasia (343), and changes in oesophageal peristalsis with maturational age (390). Oesophageal HRM-I has also recently been used to assess motility in children with intractable regurgitation, where it was successfully demonstrated to accurately diagnose and subtype rumination syndrome according to bolus movement and timing (385).

Overall, the manometry literature reflects progression from low resolution to HRM technology, and the benefits and the advantages of integrated impedance measures pertaining to bolus flow, have been outlined in the sections above (Manometry, and High-Resolution Pharyngeal Manometry with Impedance). Importantly, P-HRM-I enables an objective and dynamic assessment of swallowing pressures and the associated bolus flow patterns. P-HRM-I assessment enables measurements of contractility, distension and bolus flow timing to be derived in the pharynx and UOS. The following section describes the swallowing physiology captured by HRM and P-HRM-I and outlines the current evidence for the pressure flow parameters investigated in this research program.

2.3.1 Pharyngeal Swallowing Physiology Captured by HRM and P-HRM-I[4]

A short description of pharyngeal swallowing physiology is included here to outline the features occurring during P-HRM-I assessment. Appendix 1 provides further detail of the physiological components and neural control of paediatric swallowing. In short, neural control of swallowing requires central pattern generators (CPG) of the brain stem to receive sensory inputs from the oral cavity and oropharynx in order to modulate the pharyngeal swallowing response (223). A 'leading complex' of neuroregulation coordinates soft palate elevation and velopharyngeal pressures to seal the nasal cavity, hyolaryngeal elevation, and commencement of cricopharyngeus muscle relaxation, all to prepare the pharyngeal chamber for lingual propulsion and bolus passage (195). Once lingual propulsion of the bolus occurs, pharyngeal and UOS distension (extent and duration) are modulated to accommodate bolus characteristics, such as size, consistency and temperature (224). During pharyngeal swallowing, epiglottic deflection and vocal fold adduction protect the airway from foreign body

[4] The text in this section originates from an invited manuscript:

Ferris L, Omari T. Pharyngeal manometry in pediatric dysphagia assessment. Perspectives of the ASHA Special Interest Groups. 2019;4(4):656-82. Bibliography reference (21). Some wording changes have been made for inclusion in this thesis.

invasion. The pharyngeal stripping wave follows lingual propulsion as a bolus clearing force (24, 225, 226). With HRM, objective pressure values of pharyngeal and UOS contractility are generated. With integrated impedance, P-HRM-I generates, contractility as well as distension and bolus flow timing pressure flow parameters.

In paediatric dysphagia, manometric evaluation remains vastly underutilised compared to the adult sphere (227-231). It is likely that with increasing interest in this technique, paediatric experience, and clinical application of HRM, data across a range of OPD presentations and age groups will develop. Until such time we look predominantly to the adult literature for evidence of the physiological findings and diagnostic value of HRM in swallowing assessment.

2.4 An Overview of P-HRM-I Parameters Relative to VFSS and HRM Measurements

This section gives context to the parameters investigated in this research program by providing an overview of the metrics generated from the most established paediatric swallowing physiology assessment methods, capable of generating quantitative measurements. These are VFSS, HRM and P-HRM-I. A recent review of the instrumental approaches to paediatric swallowing assessment, highlights the value of obtaining quantitative measurements to improve assessment accuracy, aid standardisation of data interpretation, and to advance the overall understanding of swallowing physiology (232). Dharmarathna and colleagues have also outlined a full systematic review of the quantitative measurements derived by instrumental modalities in children, demonstrating that manometry provides the most objective evaluation of the pharyngeal and oesophageal swallowing phases (114). These recent publications are fundamental to the context of this research program, as they support the need to explore the parameters derived by manometry techniques for their contribution towards characterising swallowing physiology and, more specifically, the potential future use of these methods in children. Table 2.1 presented below complements such work, as it provides an indication of the spectrum of swallowing parameters from qualitative to quantitative, within each swallowing

phase. Table 2.1 shows the scope of VFSS measurements reported in recent paediatric literature (62, 81, 90, 100, 101, 233, 234), and relates them to the P-HRM-I parameters (core outcome set and other novel metrics) investigated in this research program. The HRM recently defined core outcome set metrics are included to indicate the swallowing parameters derived by pressure-only analysis (191, 235). Manometry-based modalities currently show the greatest potential to objectively assess paediatric swallowing pathophysiology (114). However, note that VFSS software-based analysis also produces quantitative parameters and its application in paediatric populations is emerging (81, 100). While comparisons across instrumental modalities are beyond the scope of this thesis, it is important to understand the swallowing parameters reported in the paediatric literature and the inter-relationships between swallowing parameters acquired across modalities. The FEES technique is employed successfully in some paediatric centres, however, at this time, the parameters measured are subjective in nature and there is little evidence for measurement reliability (114). For this reason, FEES is not included in this section. For similar reasons ultrasound is excluded from Table 2.1, however the future clinical use of ultrasound seems promising, with emerging evidence for quantifiable measurements of infant sucking, hyoid displacement and pharyngo-glottal reflex assessments (18, 129, 131).

In relation to VFSS, several temporal and displacement measurements are used to assess swallowing physiology, efficiency and safety. This enhances the objectification and standardisation of analysis outcomes (81, 90, 101, 233, 234). For example, visualisation of bolus location at initiation of laryngeal closure indicates the responsiveness of the pharyngeal swallow reflex, and oral bolus containment efficiency (233). Similarly, presence of pharyngeal residue post swallow can be interpreted as evidence for ineffective bolus clearance relating to inadequate lingual propulsion and/or pharyngeal clearing forces (101). Recent application of quantitative VFSS measures in a large cohort of 146 infants showed that residue, nasal regurgitation and oesophago-pharyngeal reflux were associated with increased (worse) pharyngeal constriction ratio (PCR) and higher (worse) bolus clearance ratio (BCR) (101).

Additionally, aspiration and a >3 sucks per swallow ratio were associated with increased total pharyngeal transit time (TPT) (101). These markers of swallowing physiology objectively describe the features associated with OPD symptoms, however the underlying biomechanics, such as pharyngeal strength, can only be inferred from visual analysis (90, 99, 101). In comparison, HRM and P-HRM-I techniques indicate swallowing efficiency and safety according to pressure, distension and bolus flow measures (184), which specifically indicate biomechanical features that either facilitate or impede bolus passage. For example, pathology leading to elevated UOS relaxation pressure increases bolus resistance and impairs bolus flow through the UOS zone, which leads to an increased risk of residue and airway invasion (189, 195, 216). To indicate overall swallowing risk and safety, P-HRM-I derives a global measure, the swallowing risk index (SRI). The SRI incorporates the proficiency of a set of parameters previously shown to correlate significantly with radiological evidence of aspiration (153, 236). These are pharyngeal bolus presence time, hypopharyngeal intra-bolus pressures, pharyngeal contractility, and the pharyngeal distension to contraction latency (153, 236). Additionally, a global measure of residue, the post swallow impedance ratio (PSIR), has also been reported (237).

In relation to the layout of all parameters in Table 2.1, VFSS metrics are presented in the first column under the following subheadings: *timing measures*, *displacement measures,* and *descriptive measures* (101). As the focus test of this research program, P-HRM-I parameters are positioned in the middle column of Table 2.1 to assist the reader with cross referencing between VFSS and HRM parameters. The P-HRM-I pressure flow parameters are presented as they relate to the anatomical/physiological measurements derived by VFSS. The HRM pressure parameters positioned in the third column demonstrate which measurements are derived by HRM and P-HRM-I modalities (in these cases cells in Table 2.1 are merged), and which measurements are unique to P-HRM-I (in these cases, HRM cells are unfilled). It is proposed that swallowing parameters fit along a spectrum of objectivity in the following order: qualitative ⇨quantifiable ⇨or quantitative, according to the following definitions:

- *Qualitative* parameters (coded in yellow) are defined as measures that rely on the description of a swallowing feature that is solely based on an assessor's visual judgement, as seen in traditional VFSS analysis, e.g. lip seal competence (234).
- *Quantifiable* swallowing parameters (coded in blue) refer to manually produced numerical ratings or calculations of swallowing features based on visual analysis of image-based instrumentation, generated in the absence of automated software. Examples include bolus location at initiation of laryngeal closure (1=oral cavity, 2=BOT/valleculae, 3=pyriform sinuses/CP sphincter, 4=other) (233), and the well-established PAS rating (outlined in Appendix 1 (68).
- *Quantitative* parameters (coded in green) are defined as those measures that are objectively derived by a semi-automated system, which produces a numerical value, e.g. hypopharyngeal intra-bolus pressure derived by P-HRM-I analysis software (238) or maximum pharyngoesophageal segment diameter (PESmax) derived by VFSS analysis software (99).

Table 2.1. ***Swallowing Parameters Derived by VFSS, P-HRM-I and HRM Methods***

VFSS swallowing parameters	P-HRM-I parameters	HRM parameters
ORAL PREPARATORY PHASE		
Descriptive measures		
Lip seal competence Sales et al (248)		
Lingual coordination Weckmueller et al (67)		
Rhythmicity of jaw movements Weckmueller et al (67)		
ORAL PHASE		
Timing measures		
Suck time Gosa et al (247)		
Oral transit time Gosa et al (247)		
Descriptive measures		
Bolus containment/control Sales et al (248)		
Coordination oral structures during oral transit Sales et al (248)		
Efficiency of lingual propulsion	Pharyngeal distension contraction latency Ferris et al (251)	
Tongue base retraction Martin-Harris et al (91)	Mesopharyngeal contractility Omari et al (192)	
Jaw position at initiation of tongue propulsion Gosa et al (247)		
Jaw position at max pharyngeal constriction Gosa et al (247)		
Jaw position at UOS closure Gosa et al (247)		
Oral residue Sales et al (248)		
Descriptive sucking efficiency measures		
Suck/swallow bolus control Martin-Harris et al (91)		

Initiation of nutritive sucks Martin-Harris et al (91)		
Nutritive sucking rhythmicity Martin-Harris et al (91)		
Bolus location at swallow initiation Martin-Harris et al (91)		
Timing of initiation of pharyngeal swallow Martin-Harris et al (91)		
Total swallows to clear the bolus Sales et al (248)	UOS max. admittance Omari et al (192) to indicate swal. sequences	
Number of sucks per swallow Gosa et al (247)		
PHARYNGEAL PHASE		
Timing measures		
Timing of initiation of pharyngeal swallow Martin-Harris et al (91)		
Pharyngeal transit time Sales et al (248)	Bolus presence time Ferris et al (257)	
Duration of velopharyngeal closure (VP closure) Dharmarathna et al (102)	Velopharyngeal contractility Omari et al (192)	
Initiation (onset) of velar movement Gosa et al (247)		
Oropharyngeal transit time (OPT) Leonard & Kendall (83)		
Hypo-pharyngeal transit time (HPT) Leonard & Kendall (83)		
Total pharyngeal transit time (TPT) Leonard & Kendall (83)	Bolus presence time Ferris et al (257)	
UOS opening duration Gosa et al (247)	UOS relaxation time Omari et al (192)	
Time to laryngeal vestibule closure Gosa et al (247)		
Duration of laryngeal closure Gosa et al (247), Henderson et al (82)		
Pharyngoesophageal segment opening duration (PESdur) Leonard & Kendall (83)	UOS relaxation time Omari et al (192)	
Displacement measures		
Palatal-pharyngeal approximation Martin-Harris et al (91)	Velopharyngeal contractility Omari et al (192)	
Hyoid displacement 252		

Duration to max. hyoid elevation Martin-Harris et al (91)		
Laryngeal excursion	UOS apogee	
Tongue base retraction Martin-Harris et al (91)	Mesopharyngeal contractility Omari et al (192)	
Maximum pharyngeal area at rest (PAs) Leonard & Kendall (83)		
Pharyngeal stripping wave Martin-Harris et al (91)	Pharyngeal contractility Omari et al (192)	
Maximum pharyngeal constriction area (PAm) Leonard & Kendall (83)		
Pharyngeal constriction ratio (PCR) Leonard & Kendall (83)		
Pharyngoesophageal segment max opening (PESmax) Leonard & Kendall (83)	UOS max. admittance Omari et al (192)	
Bolus clearance ratio (BCR) Leonard & Kendall (83)	Post swallow impedance ratio Omari et al (207)	
Descriptive measures		
Nasopharyngeal backflow (Y / N) Gosa et al (247)	Velopharyngeal contractility Omari et al (192)	
Posterior oral spillage [248]	Distension contraction latency/bolus presence time Ferris et al (257)	
Bolus location at palatal-pharyngeal approximation Martin-Harris et al (91)		
Valleculae residue Martin-Harris et al (91)		
Pyriform residue Martin-Harris et al (91)		
UOS residue/clearance Martin-Harris et al (91)		
Bolus residue scale Dharmarathna et al (102)	Post swallow impedance ratio Omari et al (207)	
Post swallow residue (Y / N) Gosa et al (247)		
Frequency of swallows in 20s Henderson et al (82)		
Airway protective measures		
Early laryngeal vestibule closure Martin-Harris et al (91)		

Late laryngeal vestibule closure Martin-Harris et al (91)		
Timing of airway entry (pre, during, post) *		
Epiglottic movement Martin-Harris et al (91)		
Bolus location at initiation of laryngeal closure Gosa et al (247)		
Laryngeal penetration location (PAS score) Rosenbek (69)		
Amount of penetration Martin-Harris et al (91)		
Frequency of penetration Martin-Harris et al (91)		
Aspiration (PAS score) Rosenbek (69)	Swallow Risk Index Omari et al (238)	
Amount of aspiration Martin-Harris et al (91)		
Frequency of aspiration Martin-Harris et al (91)		
Frequency of penetration or aspiration in 20s Henderson et al (82)		
Protective response (e.g. swals to clear, cough)		
Time to airway closure (AIRWAYcl) Leonard & Kendall (83)		
Airway closure relative to bolus reaching UOS (BP1AEcl) Leonard & Kendall (83)		
Stand-alone HRM and P-HRM-I parameters		
	UOS pre swallow pressure Ferris et al (257)	
	Pharyngeal peak pressure Omari et al (238)	
	Hypopharyngeal contractile integral Ferris et al (257)	
	UOS integrated relaxation pressure Ferris et al (257)	
	UOS intra-bolus pressure Ferris et al (257)	
	UOS peak pressure Ferris et al (257)	

	UOS contractile integral Ferris et al (257)	
OESOPHAGEAL PHASE		
Derived during pharyngeal analysis		
Oesophageal clearance	Proximal oesophageal contractile integral Ferris et al (257)	
Full motility analysis		
	Chicago Classification Singendonk et al (319)	
	Pressure Flow parameters Singendonk et al (186)	

Note. This table demonstrates swallowing parameters reported in children as measured by the gold standard VFSS, P-HRM-I and HRM assessment methods. All parameters are coded according to the concept of holding a qualitative (yellow), quantifiable (blue) or quantitative (green) value. Most centres develop protocols specific to their clinical and research practices, therefore the list of parameters included does not claim to be exhaustive, rather it aims to provide a reference for the key VFSS swallowing features reported in the paediatric literature. Additionally, this table demonstrates the context for the P-HRM-I parameters investigated in this thesis. Superscript values indicate the references used to populate the table regarding paediatric application of these parameters. References can be viewed in the thesis bibliography. For completeness, references generated during this research program have been included in the table.

In Table 2.1, the relationship between swallowing parameters across modalities is based on the common anatomical/physiological measurement, e.g., VFSS derived maximum pharyngeal constriction area (PAm) aligns with HRM/P-HRM-I derived pharyngeal contractility; and VFSS derived palatal-pharyngeal approximation aligns with HRM/P-HRM-I derived velopharyngeal contractility. The HRM and P-HRM-I parameters are predominantly coded in green as they rely on sensor and sensor electrode detected data respectively, and purpose-designed software used in this thesis program, generates pressure or pressure-impedance based quantitative parameters. While not yet definitive, there is evidence that some P-HRM-I metrics reflect features of oral phase swallowing, including mesopharyngeal contractility (coded in blue) as a measure of tongue base retraction and DCL (coded in blue) as a correlate of how well the bolus is propelled ahead of the stripping wave (239). The UOS apogee viewed on pressure topography is positioned in the table as a qualitative correlate of laryngeal elevation extent (coded in yellow), and UOS max. admittance aligns with the number of swallows required to clear the bolus (coded in blue). It is important to note that the descriptions of the swallowing mechanism differ depending on the technology utilised to derive each parameter. For example, on VFSS, UOS opening is quantitatively indicated as extent of opening in cm (PESmax), whereas HRM computes the UOS relaxation pressure, and P-HRM-I derives UOS relaxation pressure and impedance/admittance values indicating distensibility and opening extent. The value of how P-HRM-I parameters can contribute to the characterisation of swallowing biomechanics are investigated in this research program. To further illustrate the context and relationship between quantitative P-HRM-I measurements and quantitative VFSS software-derived measurements, as reported in the paediatric literature, Table 2.2 is included below. This table provides a list of the P-HRM-I parameters examined in this research, including definitions, and cross references parameters derived by VFSS software which has been applied in paediatric patients.

Table 2.2. ***P-HRM-I Measures Relative to Quantitative VFSS Parameters***

Relative VFSS measures derived by Swallowtail™	High-resolution manometry-impedance parameters derived by Swallow Gateway™ parameters		
	Abbreviation	**Definition**	**Physiological Measurement**
	Core outcome set metrics		
Maximum pharyngeal constriction area (PAm) Pharyngeal constriction ratio (PCR)	**PhCI**	Pharyngeal contractile integral (mmHg.cm.s)	An integral pressure measure of pharyngeal contractile vigour from the velopharynx to the upper margin of the UOS
	VCI	Velopharyngeal contractile integral (mmHg.cm.s)	An integral pressure measure of pharyngeal contractile vigour within the velopharyngeal region only
	MCI	Mesopharyngeal contractile integral (mmHg.cm.s)	An integral pressure measure of pharyngeal contractile vigour within the mesopharyngeal region only, and may be indicative of tongue base retraction
	HPCI	Hypopharyngeal contractile integral (mmHg.cm.s)	An integral pressure measure of pharyngeal contractile vigour within the hypopharyngeal region only
	HP IBP	Hypopharyngeal intrabolus pressure (mmHg)	The distension pressure 1 cm superior to the UOS apogee position at the time of maximum hypopharyngeal distension (indicated by impedance/admittance)
	UOS IRP	UOS integrated relaxation pressure (mmHg)	A pressure measure of the extent of UOS relaxation pressure, generated as the median of the lowest pressure in a non-consecutive 0.25 sec. window
PES opening duration (PESdur)	**UOS RT**	UOS relaxation time (s)	A measure of the duration of UOS relaxation: a pressure interval below 50% of baseline or 35 mmHg, whichever is lower
PES maximum opening (PESmax)	**UOS Max Ad**	UOS maximum admittance (milli Siemens mS)	A measure of extent of UOS opening. The highest admittance value (inverse of impedance) recorded during trans-sphincteric bolus flow
	Novel metrics and timing measures		
	UOSCI	Upper oesophageal sphincter contractile integral (mmHg.cm.s)	An integral pressure measure of UOS contractile vigour, post swallow
	UOS BP	UOS basal pressure (mmHg)	The peak pressure at the level of the UOS pre swallow
	UOS PP	UOS peak pressure (mmHg)	The peak pressure at the level of the UOS measured immediately post pharyngeal contraction
	PCI	Proximal oesophageal contractile integral (mmHg.cm.s)	An integral pressure measure of proximal oesophageal contractility
Oropharyngeal transit time (OPT)	**DCL**	Pharyngeal Distension-Contraction Latency (s)	A timing measure from maximum pharyngeal distension to the pharyngeal luminal occlusive contraction – a correlate of how well the bolus is propelled ahead of the pharyngeal stripping wave, (in milliseconds).
Total pharyngeal transit time (TPT)	**BPT**	Bolus presence time (s)	The dwell time of the bolus in the pharynx
	SRI	Swallow Risk Index	A composite score of swallow risk

Stand-alone Swallowtail measurements not included in Table 2.2: Hyoid displacement; Duration to max hyoid elevation; Hypo-pharyngeal transit time (HPT); Max. pharyngeal area at rest (PAs); Time to airway closure duration (AIRWAYcl); Coordination of airway closure with bolus reaching PES (BP1AEcl).

Note. This table presents the P-HRM-I parameters and definitions derived by Swallow Gateway™ software and aligns the VFSS parameters derived by Swallowtail software, Belldev Medical, Illinois, USA.

Currently, there is limited evidence and the application of pharyngeal P-HRM-I parameters in the paediatric field is insufficient. Therefore, this thesis aims to develop a deeper understanding of the P-HRM-I measures for characterisation of pharyngeal physiology, and further test the measurements of luminal occlusive pressures, hypopharyngeal intra-bolus pressures, UOS opening and relaxation in relation to paediatric OPD. Having provided context for this research program by outlining the alignment of the P-HRM-I pressure flow parameters relative to the gold-standard VFSS, the following section details the research aims and objectives for the studies included in Sections 2 and 3.

Chapter 3: Research Aims and Objectives

3.1 Overall Research Rationale

This body of research aims to examine and develop an overall understanding of the value of P-HRM-I pressure flow parameters through the investigation of i) healthy swallowing physiology, and ii) paediatric OPD pathophysiology. The prevalence of paediatric OPD is increasing (20, 240, 241) and warrants the exploration of instrumental assessment methods that have the potential to increase diagnostic specificity, advance the implementation of targeted interventions and may lead to new therapies relevant to swallowing pathophysiology in the future. The P-HRM-I technique enables an objective assessment of the interaction between bolus flow and pressure generation within the swallowing mechanism. Overall, manometry techniques have been influential in the recognition of swallowing features such as pharyngeal weakness in neurological conditions and as recently demonstrated, in patients with radiation-associated dysphagia (254). Additionally, the dynamics of UOS relaxation, the impact on UOS opening extent, and the upward effect on hypopharyngeal intra-bolus pressure gradients all rely on manometric evaluation (250). HRM methods generate quantitative metrics with sound reliability (194), and have established diagnostic value in oesophageal motility assessment, now implemented as the gold standard for classification of oesophageal achalasia (140). In the future, pharyngeal swallowing classification by HRM and P-HRM-I techniques may also be possible, however comprehensive characterisation of healthy pharyngeal swallowing physiology with P-HRM-I is first required. Several studies demonstrate the capacity for P-HRM-I to describe pharyngeal swallowing biomechanics, predominantly in adult OPD (240, 241, 277). However, overall, there is a lack of P-HRM-I evidence for the description of healthy swallowing physiology, and a significant lack of evidence for the application of P-HRM-I in the evaluation of paediatric OPD. Therefore, the overarching intentions for this research program were i) to investigate the ability of P-HRM-I based pressure flow parameters to characterise

swallowing physiology; and ii) to explore the application of P-HRM-I in the evaluation of paediatric OPD.

The significance of this research relates to the potential clinical value of characterising pharyngeal pathophysiology according to quantitative biomechanical features of contractility, distension, and efficiency of bolus flow through the pharynx and UOS. There is a school of thought suggesting that OPD evaluation methods have surpassed our ability to treat and manage paediatric dysphagia (3). However, the exploration of swallowing physiology and pathophysiology with novel pressure flow parameters may improve our understanding and appreciation of deglutition at the biomechanical level, and may enhance descriptions of specific pathophysiology that could, in time, lead to the development of more targeted compensations and rehabilitation techniques. The following section outlines the research aims, questions, hypotheses and rationale for the research studies conducted and reported in this thesis.

3.1.1 The Impact of Bolus Volume and Catheter Diameter: Chapter Five

3.1.1.1 Research Aims

1. To quantify healthy pharyngeal swallowing modulation in response to altered bolus volume using pressure flow parameters generated by purpose designed AIMplot analysis
2. To quantify the effect of catheter diameter on healthy adult pharyngeal swallowing measured with pressure flow parameters generated by purpose designed AIMplot analysis

3.1.1.2 Research Questions

1. Which pressure flow parameters are altered by change in bolus volume?
2. Which pressure flow parameters are affected by catheter diameter?

3.1.1.3 Hypotheses

1. Pressure flow parameters indicative of distension will be most altered by increased bolus volume
2. Pressure flow parameters indicative of pharyngeal and UOS contractility will be most affected by the change in catheter diameter

3.1.1.4 Rationale and Significance

It is well established that pharyngeal contractility measures are altered by increased bolus volume (59, 242). Additionally, catheter diameter is known to impact contractility measures of oesophageal luminal muscles (195, 224, 243). Currently it is not known how P-HRM-I based pressure flow parameters in healthy, young adults are modified by bolus volume and catheter diameter. It is critical to determine the impact of catheter diameter on pharyngeal pressure flow parameters to ascertain the significance of catheter specifications when interpreting all pharyngeal manometry data. Additionally, characterisation of healthy swallowing physiology by P-HRM-I methods may enhance what is known of healthy pharyngeal swallowing physiology and neuromodulation. The information revealed may be used to interpret future P-HRM-I studies.

3.1.2 Swallowing Modulation to Bolus Volume and Viscosity: Chapter Six

3.1.2.1 Research Aims

1. To further quantify healthy pharyngeal swallowing modulation in response to a (wider than previously studied) range of bolus volume and viscosity conditions using pressure flow parameters generated by advanced, purpose designed Swallow Gateway™ analysis

3.1.2.2 Research Questions

1. Which pressure flow parameters are altered by increased bolus volumes and viscosity levels?

3.1.2.3 Hypotheses

1. Distension and bolus flow timing parameters will show the greatest change in response to increases in bolus volume and viscosity levels

3.1.2.4 Rationale and Significance

With advances in the purpose designed analysis software, this study builds upon the findings of Chapter 5 in order to comprehensively characterise healthy pharyngeal swallow modulation to a wider than previously reported range of bolus conditions. The reference values generated in this study may be used as a benchmark of healthy swallowing modulation to alterations in bolus volume and viscosity levels and may be used for comparison with pressure flow parameters in patients with OPD.

3.1.3 Piecemeal Deglutition During P-HRM-I and Establishing an Analysis Approach: Chapter Seven

3.1.3.1 Research Aims

1. To determine the effect of piecemeal deglutition (PD) on P-HRM-I pressure flow parameters
2. To establish a swallow selection approach for analysis of PD on P-HRM-I recordings
3. To characterise PD swallow sequences in children (under 4 years)

3.1.3.2 Research Questions

1. Which pressure flow parameters are altered by PD?
2. Which swallow should be selected for analysis from a PD swallow sequence?
3. What types of PD swallowing sequences are observed in children (under 4 years)?

3.1.3.3 Hypotheses

1. Changes in pressure flow parameters in PD will align with the changes seen in response to swallowing smaller bolus volumes
2. The most suitable swallow for analysis may not be the first swallow in a PD sequence
3. Impedance/admittance curves can be used to guide swallow selection for PD analysis
4. Older children will display fewer swallows in a PD sequence compared to younger children

3.1.3.4 Rationale and Significance

The impact of PD on swallow analysis needs to be determined, as this is a common feature of paediatric P-HRM-I recordings. To date, P-HRM-I analysis of PD swallowing relied on selection of the first swallow following bolus administration. However, it is critical that analysts identify the swallow that is most representative of a child's swallowing function, i.e., the swallow that carries the largest portion of the bolus. Impedance/admittance curves that track pharyngeal bolus flow may be used to guide selection of the most appropriate swallow for analysis. Additionally, identifying the prevalence of PD swallowing sequences may provide a description of paediatric piecemeal patterns observed in early childhood, relative to the standardised bolus volumes usually employed during the P-HRM-I recordings.

3.1.4 Paediatric OPD and Correlations with Clinical Measures: Chapter Eight

3.1.4.1 Research Aims

1. To compare pressure flow parameters in a cohort of children with OPD compared to a control group
2. To correlate pressure flow parameters with clinical measures of OPD in children

3.1.4.2 Research Questions

1. Which pressure flow parameters differentiate children with OPD from controls?
2. In children with OPD, which pressure flow parameters correlate most significantly with clinical measures of OPD?
3. Which pressure flow parameters differentiate children with overt signs of OPD from those without overt signs of OPD?

3.1.4.3 Hypotheses

1. Pressure flow parameters indicative of increased swallowing dysfunction will differentiate patients with OPD from the control group
2. An increased severity of OPD reflected by clinical measures will correlate with elevated swallow risk index (SRI) and post swallow impedance ratio (PSIR) parameters
3. Pressure flow parameters indicative of increased swallowing dysfunction will differentiate patients with and without overt signs of OPD

3.1.4.4 Rationale and Significance

To highlight preliminary markers of pathophysiology in paediatric OPD it is important to detect the pressure flow parameters which distinguish abnormal contractility, distension and/or bolus flow timing in relation to standardised clinical measures. Correlating P-HRM-I pressure flow parameters with clinical measures of OPD is a step towards a deeper understanding of the clinical value of P-HRM-I in children. Measuring paediatric OPD with quantitative pressure flow parameters may enhance the description of the underlying pathophysiology associated with symptoms and may guide future implementation of targeted rehabilitation or compensations.

3.1.5 Repeat P-HRM-I Testing in Children: Chapter Nine

3.1.5.1 Research Aims

1. To explore the impact of growth and development in children with stable medical conditions and OPD symptoms, using repeat testing of P-HRM-I methods at two time points over a 12-month period
2. To determine factors which influence repeat testing, return rate and acquisition of analysable data in a paediatric cohort
3. To apply the new core outcome set metrics (as per 2020 consensus) and new analytical methods via Swallow Gateway™ in a pilot set of paediatric data

3.1.5.2 Research Questions

1. What factors influence return rate of participants?
2. What factors influence acquisition of analysable data?
3. Which pressure flow parameters are altered between visit 1 and visit 2?

3.1.5.3 Hypotheses

1. For the exploratory, qualitative analysis of research Q1, no hypothesis was formulated
2. Bolus conductivity and patient tolerance will be the predominant factors influencing analysable data acquisition
3. Pressure flow parameters indicative of contractility and distension will be most altered between visits, suggestive of alterations occurring with growth and development

3.1.5.4 Rationale and Significance

To optimise acquisition of analysable data for ongoing management of patients with OPD it is important to identify factors influencing successful completion of P-HRM-I studies in children. To track swallowing function over time in relation to paediatric growth/development, disease progression and/or determining therapeutic intervention outcomes, diagnostic swallowing assessments need to be repeatable. Therefore, the repeatability of P-HRM-I and observed changes in paediatric swallowing function over time need to be determined.

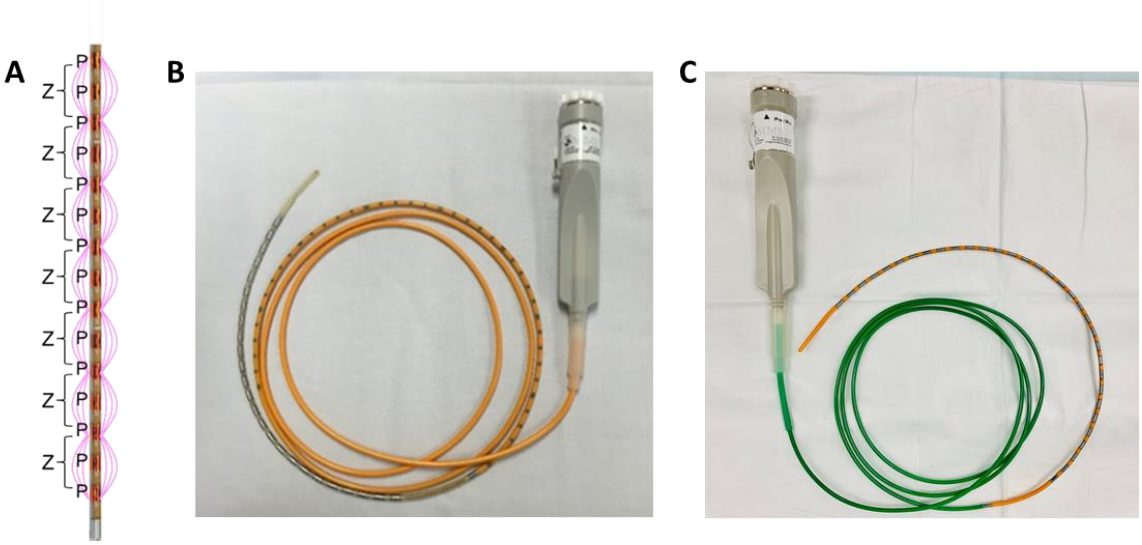
Chapter 4: Overview of Methods

The general P-HRM-I methods employed across the five prospective studies in this research program are outlined here. The more specific methods applied in the context of each individual study protocol, are outlined in each respective Chapter within Sections 2 and 3.

4.1 Catheter Specifications

Medical Measurement Systems (MMS) LABORIE, P-HRM-I unidirectional solid-state catheters were used in all studies reported in this thesis. Prior to each study, the catheter was calibrated at room temperature within a water bath for a minimum of 10 minutes. This allowed all sensors to zero at these conditions prior to in-vivo data collection. The integrated technologies of pressure and impedance within a single catheter is shown in Figure 4.1, Panel A. Catheter outer diameter or gauge is described as French (Fr). A 10 Fr catheter has an outer diameter of 3.2mm, and an 8 Fr catheter has an outer diameter of 2.7mm. Figure 4.1 displays the catheter specifications utilised in this research program.

Figure 4.1. ***High-resolution Manometry Impedance Catheters utilised in this Research***



Note. Catheter specifications utilised in this thesis. Panel A denotes pressure as P, and impedance as Z segments along the catheter. Panel B shows a 10French 25P12Z catheter. Panel C shows an 8French 32P16Z catheter.

4.1.1 HRM and P-HRM-I Core Outcome Set Metrics

A proposed set of core outcome metrics for HRM assessment inclusion has recently been described by an international working group (191). Therefore, the oropharyngeal swallowing metrics included in this thesis will be discussed in alignment with these recent definitions. For the most part, the core outcome set metrics describe four key types of biomechanical phenomena: lumen occlusive pressures at the velopharynx, mesopharynx, hypopharynx and UOS; hypopharyngeal intra-bolus pressures; UOS opening duration and extent; and UOS relaxation pressures. These metric classes are discussed below.

4.1.1.1 Luminal Occlusive Pressures

Pharyngeal and UOS lumen occlusive pressures quantify biomechanical measures of swallow strength. We know that velopharyngeal pressures modulate with increased bolus volume and viscosity (146, 159, 167, 195, 224, 244), with altered head position (151, 245), and with swallow

manoeuvres (151, 200, 246). Conversely, peak pressures of the hypopharynx are largely *un*affected by swallowing conditions such as bolus volume and full body inversion (245), suggesting a stereotypical neuroregulation of the pharyngeal stripping wave (146, 151, 235, 244). As a result, when correlated with aspiration status, hypopharyngeal occlusive pressures alone are not accurate predictors of dysphagia symptoms such as aspiration (202). However, there are some cases where pharyngeal peak pressures have been reported as abnormal in patient vs. control groups (236, 247) and maximal velopharyngeal pressures <180mmHg have been significantly associated with abnormal VFSS parameters, such as delayed swallowing response and impaired laryngeal elevation (193). Pharyngeal weakness particularly should prompt further investigation of neuromuscular disorders, as pharyngeal contraction abnormalities are relatively rare (59). In paediatric contexts, true normative reference ranges to indicate abnormal findings are unobtainable for ethical reasons, however emerging studies (54, 184, 235) in patient groups with and without OPD can begin to guide clinical findings. To illustrate the clinical application of P-HRM-I and the evident lumen occlusive pressures, case example of a 7yr old boy with muscular dystrophy and evident pharyngeal weakness is shown in Appendix 3.

4.1.1.2 Hypopharyngeal Intra-bolus Pressure

Pressure detection using P-HRM-I can derive a hypopharyngeal intra-bolus pressure (IBP), an important marker for bolus flow resistance. When elevated, this metric usually indicates an inability to modulate swallowing for larger and thicker boluses (224) and may also indicate up-stream effects from a non-relaxing UOS zone. Hypopharyngeal IBP calculates a symmetrically generated bolus distension pressure (159) with proven clinical value for detecting restricted flow (247, 248). In the only paediatric study of concurrent HRM and VFSS, pharyngeal IBP was significantly increased in aspirating patients (184). See Appendix 4 for a case example of a 5yr old boy with spastic quadriplegic cerebral palsy and silent aspiration on VFSS. In this case, elevated hypopharyngeal IBP is likely caused by premature spillage, attempted lingual propulsion and a delay in pharyngeal and UOS accommodation of the moving bolus.

4.1.1.3 UOS Opening

UOS opening is complex in nature and relies on efficient lingual propulsive forces, laryngeal elevation extent, and cricopharyngeal (CP) muscle relaxation (195). In patient groups with reduced UOS opening on VFSS, a differential diagnosis of failed UOS relaxation vs. poor UOS opening (due to impaired lingual propulsion and/or laryngeal elevation) is necessary. In the first instance, UOS opening extent will most likely be visualised with VFSS, however it is now recognised that intraluminal impedance also provides a measure of flow across the UOS zone (181, 182, 224). Abnormal impedance recordings are a non-specific marker of UOS dysfunction (249) and causes for reduced UOS opening can be further investigated with other manometry metrics.

Separately, UOS impedance readings can also assist manometry analysis of piecemeal swallowing, a common feature in infants and young children. In the context of multiple swallow sequences recorded with manometry, the impedance signal can be used to differentiate bolus swallows from saliva swallows. Therefore, across a sequence of swallows which follow from the time the bolus was given, the impedance signal can guide selection of the swallow containing the largest amount of bolus in order to provide the most meaningful result of swallow capability (183). The implications of PD during P-HRM-I studies is discussed in Chapter 7.

4.1.1.4 UOS Relaxation Pressure

UOS relaxation pressure indicates UOS distension (the pressure at full opening extent) in relation to bolus flow (167, 224, 244). In other words, during bolus flow, relaxation pressure describes the intra-bolus pressure across the UOS zone. Naturally, UOS relaxation pressure is elevated with larger bolus size, but is also increased in OPD patients vs. controls (192, 224, 250) and reduced UOS relaxation duration shown to correlate with impaired laryngeal elevation, residue at pyriform sinuses and airway invasion on VFSS (193). De-activation of the CP muscle is an important determinant of UOS relaxation pressure (192, 224, 250). Therefore, UOS relaxation pressures provide insight into the activation state of the CP muscle segment.

Clinically, impaired UOS relaxation and elevated pharyngeal IBP can be used as markers of UOS resistance and have been shown to differentiate paediatric patients with and without overt clinical signs of OPD (54). Due to the broad aetiologies of the group studied, the full mechanism for these findings requires further investigation (54). In selected paediatric case studies, such as in velocardiofacial syndrome and evident UOS relaxation failure, manometry techniques have guided decision making in regard to eligibility for, and outcomes from, dilatation, botulinum toxin (botox) therapy and myotomy (251-254). See Appendix 5 for a case example of a 5-month-old boy with UOS obstruction and frank aspiration on VFSS. Manometry investigation was required to confirm a UOS obstruction prior to successful botox therapy.

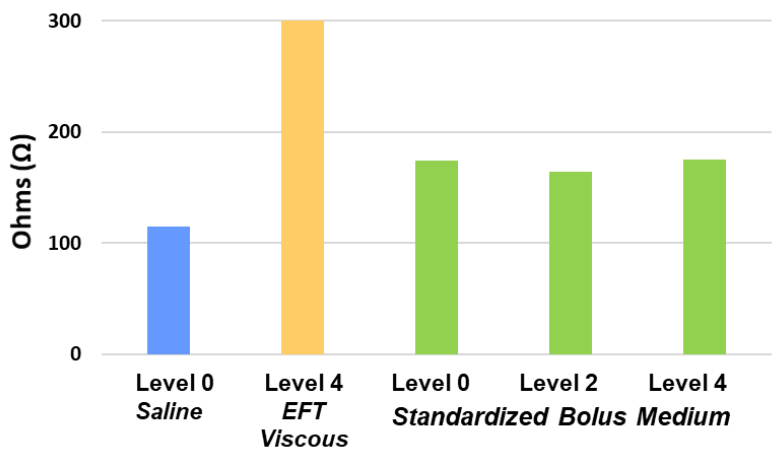
In summary, this section has outlined the current evidence for use of P-HRM-I parameters recently defined as the core outcome metrics (191). A set of additional to core outcome set metrics have also been investigated in this research program, generated by AIMplot or Swallow Gateway™ analysis. These additional to core outcome set metrics will be outlined and defined in the overview of methods section, in Chapter 4 (Table 4.1). The following section provides an overview of how P-HRM-I parameters investigated in this research relate to measurements derived by the gold standard VFSS. HRM only measurements are included to illustrate pressure measurements generated without integrated impedance data.

4.2 Bolus Preparations

In the studies reported in chapters 5, 7, 8 and 9 standard saline (0.9% NaCl) was utilised for thin fluid (IDDSI level 0) bolus swallowing. The commercially available EFT (esophageal function test) Viscous product (IDDSI level 4) for viscous boluses was utilised in accordance with MMS recommendations and is presented in Chapter 9 (chapters are presented in a sequence that best conveys the thesis narrative rather than chronologically). Later in the research program (2017), the Flinders University Manometry Swallowing Group developed an apple flavoured Swallow Bolus Medium kit (SBMkit™) in collaboration with Trisco Foods, Ltd and was used in Chapter 6 for IDDSI level 0, 2 and 4 bolus products. Appendix 7 outlines the instruction manual developed and utilised by the Flinders University Manometry Swallowing Group for SBMkit™ bolus preparations.

Bench testing results of all bolus preparations in this research program are shown in Figure 4.2, according to conductivity measured in ohms (Ω), for saline, EFT Viscous and SBMkit™ preparations at IDDSI levels 0, 2 and 4. Bench testing results for SBMkit™ preparations for IDDSI level 0, 2, and 4 were acquired and averaged from five different bottles taken from five different batches of SBM solution. Low impedance values seen for saline and the SBMkit™ preparations indicate less resistance to the electrical current between impedance electrodes, therefore signify more appropriate bolus preparations for P-HRM-I recordings. Also, the uniformity in conductive properties of SBMkit™ bolus consistencies enhance the reliability of bolus flow measurements during P-HRM-I investigations (255, 256). For these reasons, the SBMkit™ has replaced the use of standard saline and EFT Viscous in all centres acquiring P-HRM-I recordings in Adelaide, Australia.

Figure 4.2. ***Conductivity of Bolus Preparations used in this Research***

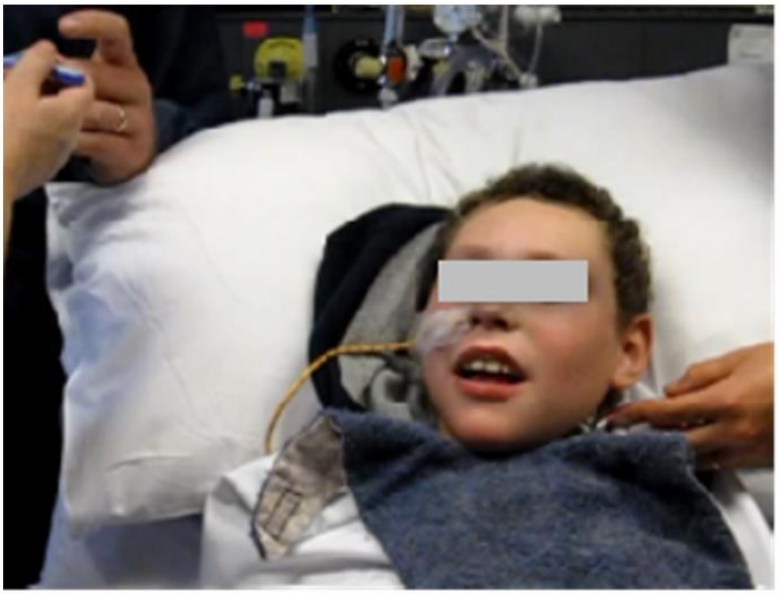


Note. This figure shows the averaged impedance values across the final 3 electrodes of an 8Fr catheter. Impedance measurements in ohms (Ω) are presented for each IDDSI level bolus preparation, indicating the resistance to the electrical current within the catheter.

4.3 Data Collection

In preparation for catheter placement, lidocaine spray (5%) was applied to the most patent naris of each healthy adult participant. The use of local anaesthetic has been discussed within the literature, with effects on swallowing parameters reported in one study (257), and no effect on swallowing risk found in another study which also reported significant improvement in tolerance when the local anaesthetic was used (258). For the paediatric studies in this research program, local anaesthetic spray was avoided as its administration has been found to unsettle children, and the impact of local anaesthetic on paediatric swallowing is not established. In a small number of the children included in Chapter 6, lidocaine spray (5%) was applied to the entrance of the nose only. In all participants (adults and children), a water-based lubricant was applied to the catheter to assist with its positioning. Once confirmed by pressure topography to have reached the appropriate position, the catheter was taped to the participant's cheek (adult or child) and secured loosely to the clothing on their back. This optimised comfort and minimised catheter movement. Figure 4.3 shows a child seated upright on the clinic bed with the catheter in situ. A key benefit of the P-HRM-I procedure is that small children can be held by a caregiver during the procedure, may be positioned in a regular highchair; see Figure 4.4, or may remain seated in their wheelchair; see Figure 4.5. Each participant was given a 5-minute accommodation period prior to commencing bolus trials. Bolus size was measured and administered to the oral cavity via syringe. A small number of children received the measured bolus via spoon. The specific bolus protocols are outlined in each chapter.

Figure 4.3. ***Paediatric Participant with Catheter in-situ***



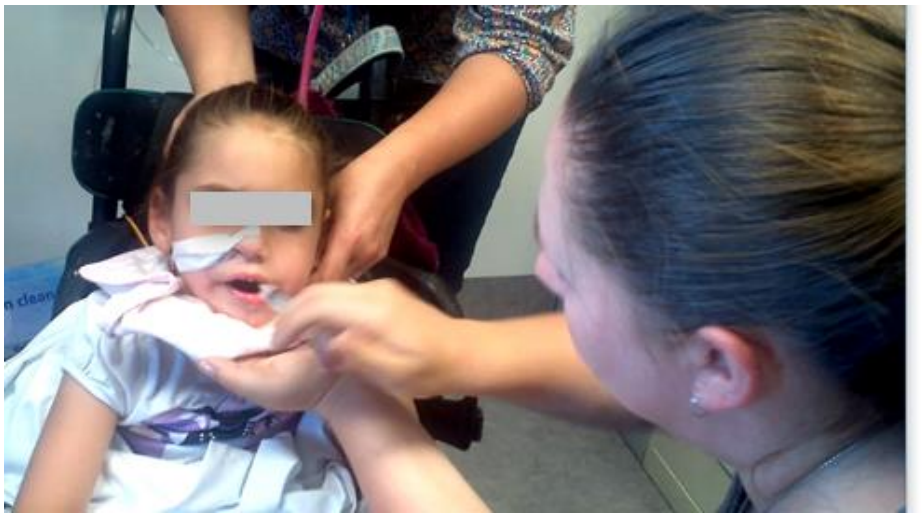
Note. Seven-year-old male participant with spastic quadriplegic cerebral palsy, seated upright on the clinic bed. 10Fr catheter positioned in right nostril. Cervical auscultation was used to facilitate detection of swallow response to the orally administered bolus. Parent consent was obtained to present this image.

Figure 4.4. ***Participant Studied while Seated in a Highchair***

IMAGE REMOVED FOR PUBLICATION

Note. Parent consent was obtained to present this image for examination but not for publication. This figure illustrated a 20-month-old boy with no known cause for OPD, seated in a regular highchair during the manometry procedure.

Figure 4.5. ***Participant Studied While Positioned in a Wheelchair***

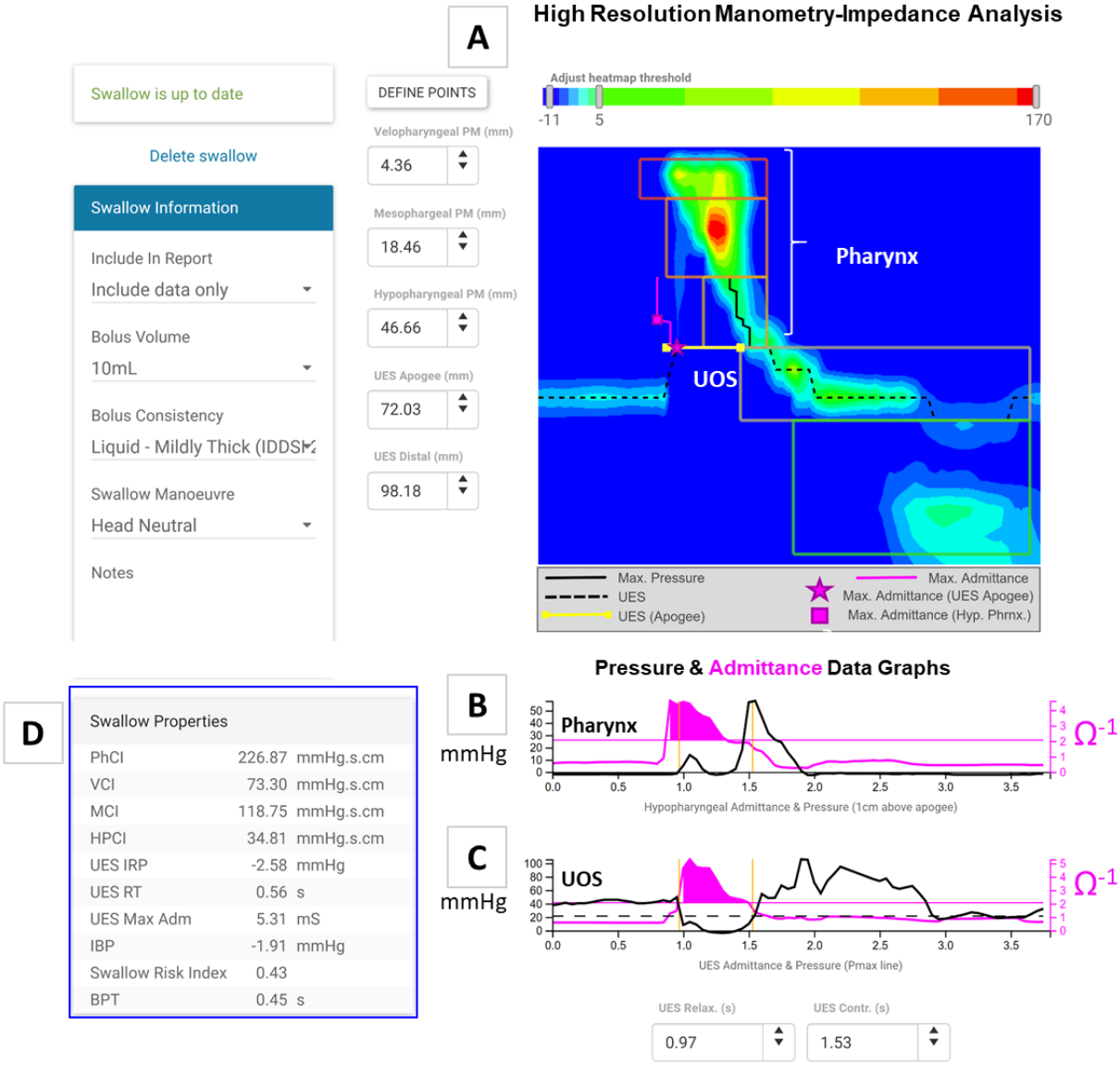


Note. This figure illustrates a 5-year-old girl with spastic quadriplegic cerebral palsy, receiving a 3ml saline bolus from a syringe, administered by her mother with evidence of anterior spillage. SP using cervical auscultation to monitor breath sounds and determine timepoint of pharyngeal swallow initiation for documentation within P-HRM-I recording. Parent consent was obtained to present this image.

4.4 Analysis Methods of P-HRM-I Used During this Research Program

Following the completion of each P-HRM-I investigation, data from swallows were uploaded to the relevant analysis platform. Analysis in Chapters 5, 8 and 9 utilised AIMplot software (54, 239, 244) and Chapters 6 and 7 utilised the Swallow Gateway™ portal (183). Swallow Gateway™ is an online application (https://swallowgateway.com/) owned and serviced by Flinders University, Adelaide, South Australia. The Swallow Gateway™ application requires that P-HRM-I studies are uploaded as an entire American Standard Code for Information Interchange (ASCII) file. Swallows for analysis are then individually selected within the application. Each swallow can be opened individually and viewed according to its pressure topography with embedded impedance data. Each swallow may be labelled/deleted/reproduced as needed during analysis. The Swallow Gateway™ program employs algorithms to define pressure flow parameters. Similar to the previously used AIMplot software, various swallow landmarks are defined and regions of interest (ROIs) are demarcated. However, advances in the analysis method means that Swallow Gateway™ requests additional landmarks as follows: velopharyngeal proximal margin, mesopharyngeal proximal margin, hypopharyngeal proximal margin, UOS apogee, and UOS distal margin. Five ROIs then appear on the topography plot; see Figure 4.4. Once the assessor has defined the points relevant to the ROI, the Swallow Properties are automated; see Figure 4.4, panel D. These values define the pressure flow parameters (also referred to as pressure flow parameters) for each swallow.

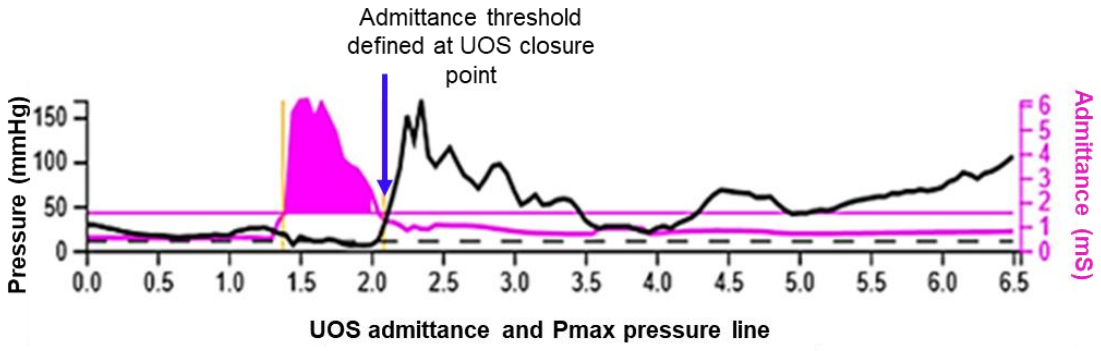
Figure 4.6. ***Swallow Gateway™ Pressure Topography and Swallow Properties***



Note. Example of a healthy participant pressure topography swallow plot. Panel A: Points are defined during analysis to generate regions of interest (ROI). Panel B: Integrated pharyngeal pressure profile and impedance/admittance curves. Panel C: Integrated UOS pressure profile and impedance/admittance curves. Panel D: Swallow Properties indicating pressure flow parameters for the swallow. Note that Swallow Gateway™ uses American spelling.

A key advancement of the Swallow Gateway™ platform (compared to previously used AIMplot) is the conversion of all impedance recordings to their inverse product: admittance (mS). This allows bolus flow (admittance) wave forms to be observed in a more logical manner with the advantage of displaying a linear relationship to luminal area, i.e., instead of impedance curves, which indicate bolus flow according to a *fall* in resistance to the electrical current between segments, admittance curves indicate a *rise* in admittance as was shown in Figure 2.10. Additionally, for each swallow, an admittance threshold is calibrated at UOS closure to ensure that admittance values at or below this threshold are meaningful for an individual's bolus flow measurements; see Figure 2.10.

Figure 4.7. ***The Admittance Threshold for Meaningful Bolus Flow Analysis***



Note. This figure demonstrates the integrated pressure and admittance waveforms detected through the UOS zone during swallowing of a conductive bolus. The blue arrow indicates the UOS closure point. The admittance threshold is calibrated at UOS closure to ensure that admittance values at or below this threshold indicate meaningful measurements of bolus flow.

These advanced analytical methods, including admittance readings are aligned with the recently defined core outcome set metrics (191). Swallow Gateway™ also generates other novel swallowing metrics, some of which have been reported in this research program. A full list of core outcome set metrics and novel Swallow Gateway™ metrics reported in this thesis is shown in Table 4.1. AIMplot software measures are included for comparison, as were reported in Chapters 5 and 8.

In summary, purpose designed algorithms underpin the semi-automated analysis methods utilised in this research program. Swallow Gateway™ is the current, and ongoing analysis platform utilised by the Flinders University Manometry Swallowing Group for P-HRM-I investigations.

Table 4.1. ***Pressure Flow Parameters Investigated in this Research Program***

Presented on the following page.

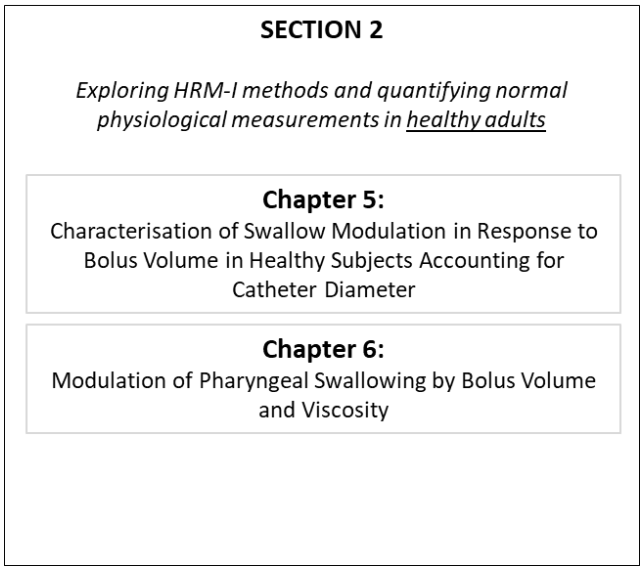
Pressure flow parameters derived in this research program					
Swallow Gateway™ portal metrics			**Previous AIMplot software equivalent metrics**		
Abbreviation	**Definition**	**Physiological Measurement**	**Abbreviation**	**Definition**	**Physiological Measurement**
Core outcome set metrics					
PhCI	Pharyngeal contractile integral (mmHg.cm.s)	An integral pressure measure of pharyngeal contractile vigour from the velopharynx to the upper margin of the UOS	**PP**	Peak pharyngeal pressure (mmHg)	Pharyngeal contractile vigour
VCI	Velopharyngeal contractile integral (mmHg.cm.s)	An integral pressure measure of pharyngeal contractile vigour within the velopharyngeal region only			
MCI	Mesopharyngeal contractile integral (mmHg.cm.s)	An integral pressure measure of pharyngeal contractile vigour within the mesopharyngeal region only			
HPCI	Hypopharyngeal contractile integral (mmHg.cm.s)	An integral pressure measure of pharyngeal contractile vigour within the hypopharyngeal region only			
HP IBP	Hypopharyngeal intrabolus pressure (mmHg)	The distension pressure 1 cm superior to the UOS apogee position at the time of maximum hypopharyngeal distension (indicated by impedance/admittance)	**PNI**	Pressure at time of nadir impedance (mmHg)	Residual pressure during max. pharyngeal distension
UOS IRP	UOS integrated relaxation pressure (mmHg)	A pressure measure of the extent of UOS relaxation pressure, generated as the median of the lowest pressure in a non-consecutive 0.25 sec. window	**UOSRES**	UOS intrabolus pressure divided by relaxation period (mmHg)	UOS intrabolus pressure during relaxation
UOS RT	UOS relaxation time (s)	A measure of the duration of UOS relaxation: a pressure interval below 50% of baseline or 35 mmHg, whichever is lower			
UOS Max Ad	UOS maximum admittance (milli Siemens mS)	A measure of extent of UOS opening. The highest admittance value (inverse of impedance) recorded during trans-sphincteric bolus flow	**UOSNI**	UOS nadir impedance (ohms)	Marker of max. bolus flow through the UOS
Novel metrics and timing measures					
UOSCI	Upper oesophageal sphincter contractile integral (mmHg.cm.s)	An integral pressure measure of UOS contractile vigour, post swallow			
UOS BP	UOS basal pressure (mmHg)	The peak pressure at the level of the UOS pre swallow			
UOS PP	UOS peak pressure (mmHg)	The peak pressure at the level of the UOS measured immediately post pharyngeal contraction			
PCI	Proximal oesophageal contractile integral (mmHg.cm.s)	An integral pressure measure of proximal oesophageal contractility			
DCL	Pharyngeal Distension-Contraction Latency (s)	A timing measure from maximum pharyngeal distension to the pharyngeal luminal occlusive contraction – a correlate of how well the bolus is propelled ahead of the pharyngeal stripping wave, (in milliseconds).	**TNIPP**	Time from nadir impedance to peak pressure (s)	Bolus propulsion ahead of the stripping wave
BPT	Bolus presence time (s)	The dwell time of the bolus in the pharynx	**FI**	Flow interval (s)	Bolus dwell time in the pharynx
SRI	Swallow Risk Index	A composite score of swallow risk	**SRI**	Swallow Risk Index	A composite score of swallow risk
			PSIR	Post swallow impedance ratio	Bolus residue score

Table Note. Table 4.1 demonstrates the abbreviations and descriptions of the pressure flow parameters derived by Swallow Gateway™ and the equivalent AIMplot software definitions and abbreviations used in studies presented in Chapters 5 and 8. The core outcome set metrics are presented in the top section of the table. The novel metrics, additional to the core outcome set metrics, explored by our research group are outlined in the bottom section of the table. All metrics presented in this table have been referred to in this research program.

This chapter broadly described the main methods utilised during this research program, regarding catheter specifications, bolus preparations, data collection, and explains the purpose designed methods of AIMplot and Swallow Gateway™ used in the research studies. The following Section 2 describes Chapters 5 and 6, which are the prospective studies conducted in healthy adult participants.

SECTION 2

Across two prospective studies, Section 2 characterises a range of physiological measures of the healthy adult swallowing response to changing bolus types and explores the effect of catheter diameter. This section was led by research questions detailed in Sections 3.1.1 and 3.1.2 relating to the impact of bolus volume and catheter diameter, and swallowing modulation to altered bolus volume and viscosity. Healthy adult volunteers were studied as true normative data are unachievable in healthy paediatric swallowing due to the ethical considerations, which protect children under the age of 18 years from research involving invasive methodology. Chapter 5 presents the preliminary findings from a cohort of 10 adults using original AIMplot software, and liquid swallows only. Chapter 6 provides an expansion of these results, according to investigations of swallowing biomechanical features in a larger cohort of 50 adults 18 to 80 years of age, across a wider range of bolus conditions, using advanced analysis software via Swallow Gateway™.



Chapter 5: Characterisation of Swallow Modulation in Response to Bolus Volume in Healthy Subjects Accounting for Catheter Diameter

This chapter will contain some repetition of material included in the literature review to reflect the necessary material needed for stand-alone publication of this chapter.

As first author of this chapter, previously published [5], I declare that I was principally responsible for writing the manuscript submitted for publication. I had 50% contribution to the experimental design of the study in collaboration with author Taher Omari (principal supervisor). I recruited all participants, acquired all high-resolution manometry with impedance studies (P-HRM-I) and completed all data analysis. I was assisted by author Taher Omari with statistical analysis and interpretation of the findings. Please see multiple author form in Appendix 8 with the statement of contribution from all co-authors of this chapter.

[5] Text in this chapter has been published as:

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. 2017; 128(6):1328-34. Minor wording changes have been made for inclusion in this thesis. Reference (233).

5.1 Introduction

Oropharyngeal swallowing is controlled and modulated via afferent inputs to primary motor cortex and brain stem (223). Bolus properties and general somatic sensory input from the oropharynx and larynx are detected via cranial nerve pathways, with feedback to the central pattern generator networks within the medulla oblongata (259, 260). These modulating inputs are integrated with information from the primary motor cortex, which is especially involved for volitional or cued swallowing (260). The modulation of the swallow motor mechanism results in coordinated timing of the swallow response with appropriate distension and contraction of the pharynx and UOS (195, 196, 223, 260, 261). This allows boluses of differing volume and consistency to transfer safely from the oral cavity into the oesophagus with little or no increase in resistance to bolus flow (195, 196, 225, 262).

Traditionally, manometry assessment has been used to profile the pharyngeal and UOS pressures generated during swallowing. Pharyngeal physiology involves coordinated movements of the velopharyngeal, hypopharyngeal and UOS regions to ensure airway protection and full bolus clearance (259). More recently manometry has been combined with impedance technology to measure and integrate bolus flow. Pressure-flow analysis (PFA) software has been developed to objectively and reliably analyse complex pressure-impedance data (153, 218, 236, 247, 249). The inverse of impedance, intraluminal admittance values, provide a reliable correlation of luminal diameter as indicated by a barium contrast column seen on videofluoroscopy, therefore providing a non-radiological alternative to track bolus presence (181, 218). Current evidence supports the notion that metrics which specifically quantify hypopharyngeal and UOS distension pressures and bolus flow timing are often altered in patients with oropharyngeal dysphagia (153, 236, 247, 249). Whilst the diameter of the recording catheter is known to alter the length tension and force generation of the oesophagus (263-265), the effect of catheter diameter on contractility, distension pressure and flow timing in the pharynx is less clear. The aim of this study was to determine, in healthy young participants, which pressure-flow measures indicate physiological neuromodulation of

pharyngeal swallowing in relation to increased liquid bolus volumes. We also aimed to observe the effect of catheter size using within-subject repeated measurements with different diameter catheters.

5.2 Materials and Methods

All investigations were performed in the Gastroenterology Department at the Women's and Children's Hospital in Adelaide, Australia. The Human Research Ethics Committee approved the study protocol (HREC 2423). Informed consent was obtained from all participants prior to commencing measurements. Inclusion criteria - no gastrointestinal medical history i.e., no dysphagia, or gastroesophageal disease. Participants underwent investigations with two catheters of differing diameters (8 and 10 French) studied consecutively on the same day in randomised catheter order. A computer-generated randomisation schedule determined which catheter was used first.

5.3 Measurement Protocol

The High-Resolution Impedance Manometry (HRM-I) catheters have pressure sensors and impedance electrodes spaced evenly across their length. The sensors detect pressures generated by swallow musculature contractions and the impedance electrodes record flow of ingested food/fluid. An electrical current is generated between two evenly spaced adjacent electrodes, referred to as one segment. The impedance within each segment differs depending on the conductivity of the surrounding environment and travelling bolus material. This study used 0.9% sodium chloride (NaCl), an optimally conductive electrolyte solution, for liquid swallows.

The 10 French catheter incorporated 36 1cm-spaced unidirectional pressure sensors and 16 adjoining impedance segments (36P16Z), each of 2 cm (Unisensor AG catheter, Attikon Switzerland). The 8 French HRM-I catheter incorporated 32 pressure sensors and 16 adjoining

impedance segments (32P12Z) (Unisensor AG catheter, Attikon Switzerland). Each catheter was positioned trans-nasally straddling the entire pharyngo-oesophageal segment. Lignocaine spray (5%) was used within the nose. A water-based lubricant was used to assist with passage of the catheter. The pressure-impedance data were acquired at 20 samples/sec (Solar GI acquisition unit Medical Measurement Systems, Enschede, The Netherlands). Participants were seated upright in the head neutral position. After a 5-minute accommodation period subjects were cued to swallow liquid saline boluses administered via syringe. Bolus volumes comprised three each of 2.5ml, 5ml, 10ml, 20ml and 30ml. On completion of the swallow protocol the catheter was removed, and the subject was re-intubated with the alternative diameter catheter and the swallow protocol was repeated.

5.3.1 Analysis of Pressure-Impedance Recordings

Pressure-impedance data for each swallow were exported in .csv file format. The extracted data file was then analysed using AIMplot, purpose designed MATLAB based software (copyright T Omari; created in MATLAB version 7.9.0.529; MathWorks Inc., Natick, MA, USA). Impedance values were converted to their inverse product, *admittance* (admittance = 1/ohms; units in millisiemens, mS). Using AIMplot, the analyst selected spatiotemporal landmarks after which the software automatically determined three separate regions of interest encompassing 1) the velopharynx and tongue base, 2) hypopharynx, and 3) UOS. Swallow function metrics were calculated within each region (see below) and were averaged per volume for each catheter configuration. The reliability of this method and the specific details of the analysis algorithms have been previously described (153, 163, 181, 218, 224, 236, 247, 266, 267).

5.3.2 Individual Swallow Function Variables

All individual swallow function variables are indicated in Figure 5.1. The *velopharyngeal tongue base contractile integral* (VCI) was based on the integral of pressures >20 mmHg within the

region of the velopharynx and tongue base during the swallow. Contractility of the pharyngeal stripping wave proximal to the UOS was calculated as the *pharyngeal peak pressure* (Peak P), defined as the maximum contraction of the pharynx. Additionally, the *UOS post relaxation peak pressure* (UOS Peak P) was determined by the maximal peak pressure up to 1 second after relaxation offset. *The distension-contraction latency of the whole pharynx* (Ph DCL) was determined for the pharyngeal region proximal to the UOS apogee position. This metric is a temporal relationship of average time from pharyngeal peak admittance to pharyngeal peak pressure. It defines the latency from maximum bolus distension to maximal pharyngeal contraction and is a marker of how well the bolus is propelled ahead of the pharyngeal stripping wave.

During bolus swallowing the maximum admittance estimates the area at the axial centre, or most distended part, of the lumen during bolus transport (218, 224, 249). Hence, pressure measured at, or the relative timing of maximum admittance is an accurate measure of pharyngeal intra-bolus distension pressure and timing of maximum distension, respectively. For this study, the intra-bolus pressure at maximum admittance, 1cm above the UOS, was used to define *hypopharyngeal intra-bolus pressure* (hIBP). This variable represents the videomanometry derived parameter *mid-bolus pressure* (159, 248). *The pharyngeal bolus presence time* (Ph BPT), indicating the bolus dwell time in the hypopharynx during the swallow, was shown by the upstroke and downstroke inflexions of the admittance curve. The maximum luminal cross-sectional area within the UES, during bolus flow, was inferred based on the *UOS maximum admittance* (UOS Max Ad) (218, 224, 249).

The *UOS basal pressure* (UOS basal P) and UOS relaxation pressure were determined using the *e-sleeve* method (145) based on the value and location of maximum axial UOS pressure over time. The *UOS integrated relaxation pressure* (UOS IRP) was defined as the median of all lowest pressures (contiguous or non-contiguous) recorded over a 0.25 sec period. *UOS Open Time* (UOS OT) was defined by the period between the upstroke and downstroke inflexions of the UOS admittance curve.

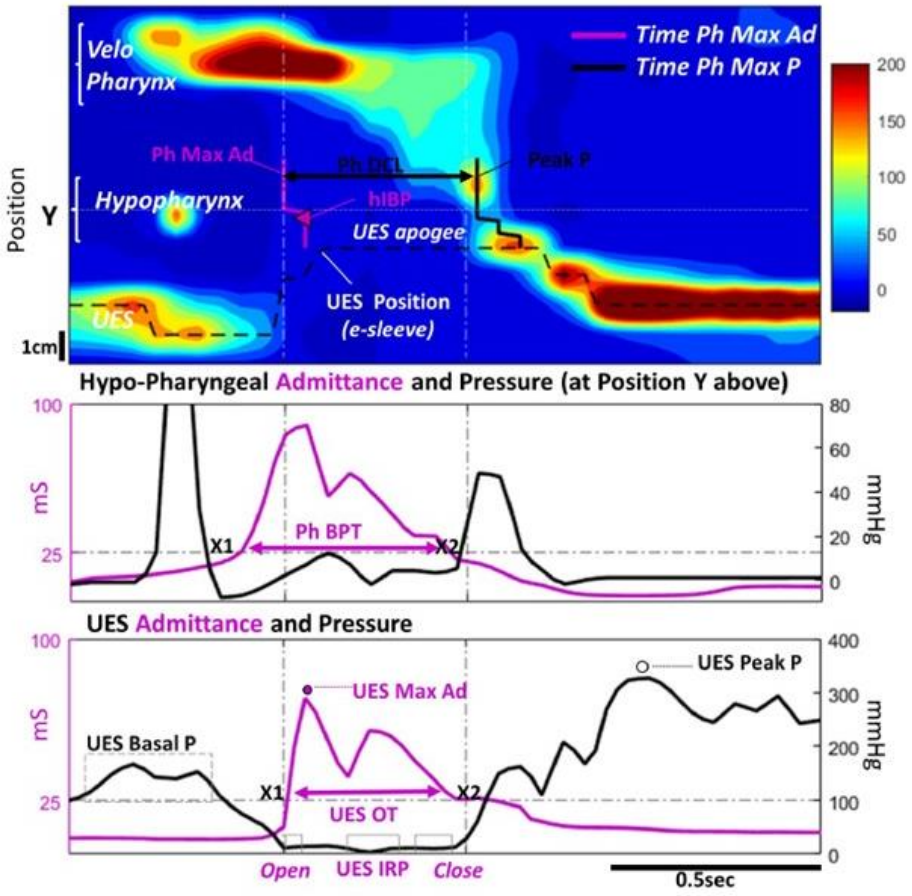


Figure 5.1. ***AIMplot derived Pressure Flow Parameters***

Note. This figure demonstrates the individual pressure flow parameters derived using Pressure-Flow Analysis with AIM*plot* software. The first step in the analysis routine was to view a complete pressure topography plot of all pressure (and embedded impedance) data for each swallow. This was followed by identification of the following landmarks: the time of Upper Oesophageal Sphincter (UOS) relaxation onset and offset and the axial positions of the velopharynx, hypopharynx, UOS apogee and UOS distal margin. The software then created a pressure topography sub-plot of the pharyngo-UOS region (see contour plot in Top Panel) which was automatically populated with the relevant analysis features allowing rapid automated calculation of 10 separate swallow function variables as follows: *velopharyngeal tongue base contractile integral* (VCI) was calculated based on pressures >20 mmHg in the region of the velopharynx and tongue base; the time of pharyngeal maximum admittance (Time Ph Max Ad) guided the calculation of pressure at maximum admittance (P Max Ad) and therefore the *hypopharyngeal intra-bolus pressure* (hIBP, at 1cm proximal of the UOS apogee position i.e. position Y); the time of pharyngeal maximum contractile pressure (Time Ph Max P) guided the calculation of *mean pharyngeal peak pressure* (Peak P) and the *pharyngeal distension-contraction latency* (Ph DCL); the axial trajectory of the UOS high pressure zone during the swallow (UOS position) determined the UOS admittance and pressure profiles (see graph in Bottom Panel) from which the *UOS maximum admittance* value (UOS Max Ad), the *mean UOS basal pressure* (UOS Basal P), the *0.25s UOS integrated relaxation pressure* (UOS IRP) and the *UOS post relaxation peak pressure* (UOS Peak P) were calculated; the *UOS open time* (UOS OT) was also estimated based on the time from rapid admittance upstroke (X1, Bottom Panel), signifying opening, to the inflexion of the admittance downstroke, signifying closure (X2, Bottom Panel); finally, the level of admittance recorded at UOS closure (i.e. the downstroke inflexion; 25mS in this example) provided an admittance threshold for estimation of the *pharyngeal bolus presence time* (Ph BPT) (see X1 and X2, Top Panel).

5.3.3 Global Swallow Function Variables

The *Swallow Risk Index* (SRI) combines four hypopharyngeal measures to derive a single value representative of global OPD and aspiration risk (59). Previous studies with simultaneous videofluoroscopy (VFSS) in adults suggest the cut off for normality is < 15 (153, 236). The SRI is derived by the following formula:

$$SRI = \frac{Ph\ BPT \times IBP}{PP \times (DCL + 1)} \times 100$$

The *post swallow impedance ratio* (PSIR) is an integrated ratio which relates post swallow impedance to the impedance during pharyngeal bolus passage. The PSIR has previously been shown to rise with post swallow pharyngeal residue seen on VFSS (236).

5.3.4 Statistical Analysis

A statistics package (IBM Corp. released 2013, IBM Statistical Package for the Social Sciences [SPSS] Statistics for Windows, v. 22.0 Armonk, NY: IBM Corp) was used to examine the data. Measurements were predominantly parametric therefore for all comparisons repeated measures ANOVA were performed using a General Linear Model with repeated volume and diameter measures. Bonferroni adjustments were incorporated for all comparisons. A p-value <0.05 was considered to indicate statistical significance. Partial Eta Squared (ηp^2) was used as a measure of effect size (ηp^2 of 0.1 = small effect, 0.3 = medium effect, 0.5 = large effect).

5.4 Results

All 10 participants (6 male: 4 female; mean age: 28 years, range 24 – 33 years) were non-smokers with no gastrointestinal medical history reported. No participants took regular medications at the time of their participation. Following randomisation, six of the participants

commenced investigations with the larger catheter. A total of 300 swallows were analysed amongst participants, across the two catheter configurations. The effects of bolus volume and catheter diameter are described below and presented in Table 5.1 and Figure 5.2. Whilst main effects of bolus volume and/or catheter diameter were seen, no volume*diameter interactions were observed for any variable; see Table 5.1.

5.4.1 Effects of Bolus Volume

Contractility measures Peak P, UOS basal P, and UOS Peak P were not affected by bolus volume; see Table 5.1, Peak P and UOS Peak P data shown in Figure 5.2. However, VCI, the pressure generated in the region from velopharynx to tongue base, significantly increased with volume; see Table 5.1 and Figure 5.2. The UOS distension area (UOS Max Ad) was significantly elevated; see Table 5.1 and Figure 5.2; pharyngeal and UOS distension pressures (hIBP and UOS IRP) were significantly higher ($p<0.05$ for both); the latency of bolus propulsion ahead of the pharyngeal stripping wave (Ph DCL) was significantly longer ($p<0.001$); and the UOS open time (UOS OT) was significantly longer for larger volumes ($p<0.05$); see Table 5.1. Of the global swallow function variables, the SRI was not affected by volume, whilst PSIR was lower with larger volumes ($p< 0.001$); see Table 5.1.

5.4.2 Effects of Catheter Diameter on PFA Metrics

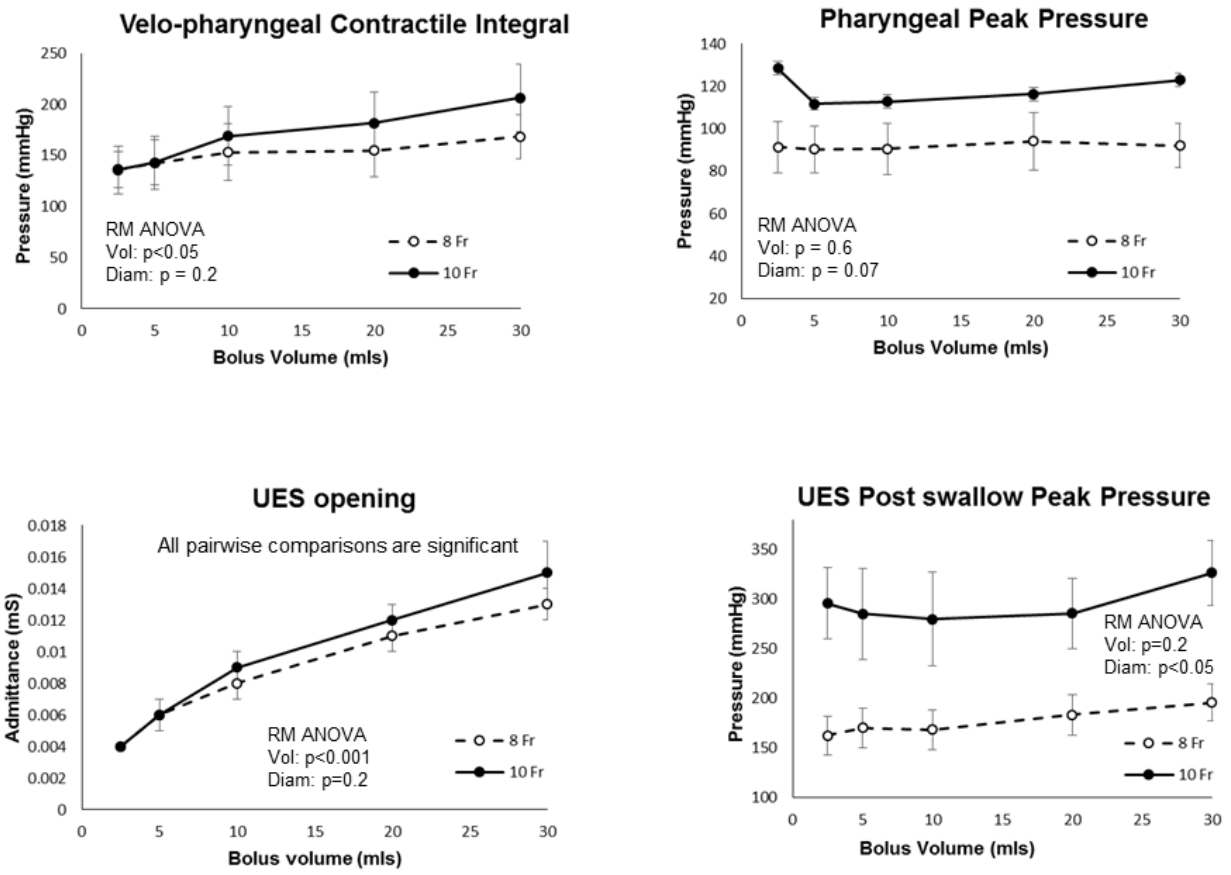
The contractility metrics of the UOS (UOS basal P, UOS Peak P) which were previously unchanged by volume were significantly greater when recorded with the larger diameter catheter; see Table 5.1. The VCI, which increased with volume, was not significantly affected by catheter diameter; see Figure 5.2. The UOS relaxation during bolus flow was significantly reduced (higher IRP, see Table 5.1) with the larger catheter. However, UOS distension area (UOS Max Ad) was unaffected by catheter size; see Table 5.1. Bolus flow timing measures were less affected by catheter size, however UOS OT was significantly shorter when assessed with the larger catheter; see Table 5.1.

Table 5.1. ***Effects of Volume and Catheter Diameter on Pressure Flow Parameters***

Variable Subtype	Variable	ANOVA parameters	Volume Effect	Diameter Effect	Vol*Di Interaction
Contractility Variables	Velopharyngeal/Tongue base Contractile Integral	*F* *P* np^2	*10.930*↑ **0.011** 0.897	2.049 ns	0.832 ns
	Pharyngeal Peak Pressure	*F* *P* np^2	0.603 ns	4.014 0.077 0.399	0.366 ns
	Upper Oesophageal Sphincter (UOS) Basal Pressure	*F* *P* np^2	1.338 ns	*18.426*↑ **0.003** 0.697	0.416 ns
	UOS Post Relaxation Peak Pressure	*F* *P* np^2	1.031 ns	*9.769*↑ **0.014** 0.550	0.284 ns
Distension Pressure Variables	Hypopharyngeal Intra-bolus Pressure 1 cm above UOS	*F* *P* np^2	*10.998*↑ **0.039** 0.936	3.950 0.094 0.397	1.196 ns
	UOS Integrated Relaxation Pressure (0.25s)	*F* *P* np^2	*10.913*↑ **0.011** 0.897	*9.433*↑ **0.015** 0.541	0.085 ns
Distension Diameter Variable	UOS Maximum Admittance	*F* *P* np^2	*56.539*↑ **<0.001** 0.978	1.959 ns	0.774 ns
Flow Timing Variables	Pharyngeal Distension-Contraction Latency	*F* *P* np^2	*36.401*↑ **0.001** 0.967	0.085 ns	0.265 ns
	Pharyngeal Bolus Presence Time	*F* *P* np^2	1.808 ns	4.246 0.073 0.347	1.573 ns
	UOS Opening Time	*F* *P* np^2	*11.572*↑ **0.010** 0.903	*8.203*↓ **0.021** 0.506	0.857 ns
Global Swallow Function Variables	Swallow Risk Index	*F* *P* np^2	1.269 ns	0.170 ns	4.202 ns
	Post Swallow Impedance ratio	*F* *P* np^2	*10.834*↓ **0.011** 0.897	1.121 ns	0.586 ns

Note. Data are main effects and interaction effects of bolus volume and catheter diameter on swallow function variables, calculated with two-way, within group analysis of variance. F = F statistic for effect; P = statistical significance; np^2 = effect size; ↑↓ indicates the direction of the effect for larger volumes/larger catheter; ns = not significant.

Figure 5.2. ***Effects of Bolus Volume and Catheter Diameter***



Note. Data are estimated marginal means (95% CI) compared with general linear model repeated measure analysis, with catheter diameter and bolus volume as covariates (Bonferroni pairwise adjustments for multiple comparisons). Swallow function variables were derived by Pressure Flow Analysis, AIMplot software. * Pairwise significance (p<0.05) vs 30mls. # Pairwise significance (p<0.05) vs 20mls. ¤ Pairwise significance (p<0.05) vs 10mls. Note American spelling in graphs generated in SPSS during preparation of this chapter for publication.

5.5 Discussion

Overall, this study highlights that swallow metrics reflecting distension pressure, distension diameter, and pressure-flow timing were affected by bolus volume, while swallow metrics reflecting lumen occlusive pressures were affected by catheter diameter. Some metrics, for example UOS IRP and UOS OT, were affected by both volume and diameter, most likely because they are metrics influenced by both distension and occlusion and/or are subject to catheter mucosal contact during swallowing. The VCI was the only purely occlusive pressure measure that was influenced by bolus volume.

In healthy participants, larger bolus volumes are known to lead to an earlier onset and extent of hyolaryngeal excursion, earlier UOS opening, greater distension diameter and longer opening duration (59, 195, 196, 224, 225). These modulated events with altered pharyngeal dilatation or distension ensure minimal flow resistance and optimal airway protection during bolus passage (195, 198). Larger volumes elicit stronger lingual propulsive forces which initiate a swallow adapted to accommodate that bolus size (198, 262). The effect of bolus volume on the occlusive pressure between velopharynx and tongue base previously reported by others (146) were clearly observed in this study; see Figure 5.2. Nonetheless, pressures in the hypopharynx and UOS remained unchanged in relation to volume challenge (195, 196, 225, 262, 268, 269), confirming that motor function of these regions during regular swallows is largely stereotypical. The oral cavity is specialised for distinguishing bolus characteristics whereas the pharyngeal contractility does not make these same distinctions (270). However, in the context of the earlier arrival of larger boluses into the pharynx (i.e., earlier pharyngeal receptive dilatation) (195, 196) ahead of the pharyngeal stripping wave, a longer pharyngeal distension-contractile latency was observed.

As anticipated, UOS distension area (inferred by admittance) was also markedly elevated when larger bolus volumes were swallowed; see Figure 5.2. This was associated with an increase in hypopharyngeal distension pressure, particularly as the ability of the pharynx to accommodate

a larger, faster moving bolus was challenged by the largest 20-30ml boluses. This suggests that the bolus area/diameter and distension pressure, when measured together, may provide a dependable physiological assessment in response to bolus volume. In patients this will likely be observed at a lower threshold and should be tested in future studies.

During swallowing UOS opening is physiologically complex and relies on cricopharyngeal (CP) muscle relaxation, along with hyolaryngeal excursion, and modified sphincter dimensions based on bolus size and compressibility (195, 196, 225). The CP muscle must deactivate for relaxation to occur, and this deactivation 'pause' is thought to be affected by bolus size (224). There was a lengthened UOS OT for larger boluses in this study, especially evident for 20 and 30mls. It has recently been shown that amongst healthy subjects, larger liquid boluses of 20ml were able to drive the UOS open, which in itself leads to CP deactivation (224, 271). Mechanoreceptors deep within the CP muscle fibres are thought to send afferent feedback via vagal pathways which activate submental muscles for longer, in turn keeping the UOS open at greater distension until the larger bolus has cleared (224). In oropharyngeal dysphagia, with insufficient extent and/or duration of UOS opening, elevated hypopharyngeal distension pressures are expected. Therefore, when there is a mismatch between the volume swallowed and the UOS opening time, the rate of trans-sphincteric flow increases and this leads to disproportionately elevated upstream pressures (195, 266). A punctuated increase in hypopharyngeal distension pressure, at a particular volume, may mark the point of failure of bolus accommodation within the swallowing mechanism (266).

Finally, in regard to catheter diameter, as expected this within-subject comparison study showed effects on a number of contractility, and some distension, metrics; see Table 5.1, Figure 5.2. We consistently recorded pressures of higher amplitude in the UOS with the larger catheter. Length tension properties of luminal muscles maintain a longer muscle length during contraction in the presence of a larger diameter catheter, therefore increasing the tension (pressure) measured (263-265). We expected the pharyngeal contractile pressure to be higher

with a larger catheter. The fact that only a statistical trend for increased pressure ($p<0.077$) was observed highlights the potential variability in this parameter.

Possible confounding factors, such as the irregular shape of the pharynx in combination with our use of unidirectional pressure sensors, could have markedly impaired pressure measurements. Thus, our potential to measure volume-related contractile pressure differences in this region may be compromised. Indeed, studies investigating the symmetry of deglutitive pharyngeal and UOS pressures using state-of-the-art 3D HRM catheters have recently been published (158, 159, 163). While it could be argued that circumferential sensors are optimal for pharyngeal manometry, the provision of circumferentially *averaged* results for each sensor is not necessarily akin to obtaining multiple separate, radially orientated readings (159). Furthermore, parameters of pharyngeal peristalsis, even when based on circumferentially averaged pressure measurements, have shown significant intra- and inter- subject variability (158) and poor test-retest reproducibility of pharyngeal contractility measurements in particular (163). As the factors driving the measured pharyngeal occlusion pressure are clearly complex, we believe a re-direction of attention to other, more reliable parameters, such as bolus distension area and pressure-flow timing is needed. Hypopharyngeal IBP and flow timing measures elucidated physiological modulation to volume challenges in this study, and as previously reported hypopharyngeal IBP is a symmetrical measure, likely due to the equalised pressures within the bolus space at this time point (159).

In the UOS zone specifically, the larger catheter detected a shorter UOS OT and a higher UOS IRP. We believe that this is most likely a result of the greater opportunity for contact between the UOS wall and the impedance electrodes/pressure sensors, due to the larger catheter circumference. As previously discussed, asymmetry may have also influenced the UOS IRP. Indeed, it has been recently shown that, unlike pharyngeal intra-bolus pressure (159), UOS relaxation pressures are asymmetrical (158).

5.6 Conclusion

This study highlights the importance of including distension, flow, and timing measures for meaningful assessment of swallow physiology and pathophysiology. Therefore, capturing key swallow modulation features using P-HRM-I assessment requires the use of optimally conductive boluses of a range of volumes, ideally up to 20ml in patients, when considered clinically safe to do so. Furthermore, inaccurate interpretation of findings may occur if pressure results are not considered in the context of the catheter characteristics used for acquisition of swallow assessment. Diagnostic reference ranges specific to catheter type and diameter are needed for reliable interpretation of oropharyngeal dysphagia assessment.

Chapter 6: Modulation of Pharyngeal Swallowing by Bolus Volume and Viscosity

Between data collection for Chapter 5 (2015) and Chapter 6 (2018), key advances in pressure flow analysis analytical methods led to the development of the Swallow Gateway™ online portal, invented by principal supervisor Taher Omari, owned by Flinders University, and co-developed and maintained in collaboration with Axios© web developers. The reliability of Swallow Gateway™ was tested in 2017, and results showed that pressure flow parameters could be reliably derived in comparison to the original AIMplot analysis. Additionally, intra- and inter-rater reliability were substantial to excellent (215). Chapter 5 utilised original AIMplot analysis and showed that swallowing alterations to distension pressures, luminal diameter and timing measures occurred as the bolus volume changed. These swallow modulatory effects sparked interest and were the primary rationale for designing a larger cohort study using advanced Swallow Gateway™ analysis methods to investigate healthy swallowing responses to a wider range of bolus conditions including viscosity. The introduction will contain some repetition of material included in the literature review to reflect the necessary material needed for stand-alone publication of this chapter.

I am first author of this chapter, now published[6]. I declare that I was principally responsible for writing the manuscript submitted for publication. I recruited all participants, acquired all high-resolution impedance manometry studies (P-HRM-I), and completed all data analysis. I was assisted by author Taher Omari with statistical analysis and interpretation of the findings. Please see the form in Appendix 8 with the statement of contribution from co-authors of this chapter.

[6] Text in this chapter has been published as:

Ferris L, Doeltgen S, Cock C, Rommel N, Schar M, Carrion S, et al. Modulation of pharyngeal swallowing by bolus volume and viscosity. Am J Physiology - Gastrointest Liver Physiol. 2021; 320(1): G43-G53. Reference (257). Minor wording changes have been made for inclusion in this thesis.

6.1 Introduction

The oropharyngeal swallow response requires complex neuro-regulation (140, 172, 196, 211, 223, 225, 236, 272). During volitional swallowing, bolus characteristics such as volume, taste, viscosity and temperature are detected and relayed to the sensory cortex, and brainstem (223).These sensory inputs enable adaptation of the swallow system for optimal bolus transfer from the oral cavity to the oesophagus.

The pressure events associated with the swallowing motor response can be recorded using pharyngeal high-resolution pharyngeal manometry (HRM) (145, 149, 150, 158, 159, 167, 209, 273, 274) and bolus flow events can be assessed when HRM is integrated with impedance measurement (153, 181, 190, 202, 209, 224, 244, 249, 250, 275, 276). Using this combined technique with automated analysis methods, a rich, objective dataset of pressure and flow measurements can be acquired and used to detect the swallow motor response in relation to bolus characteristics (59, 190, 194, 209, 215, 277). Most recently, a core outcome set of parameters and protocols for HRM with impedance assessment has been suggested (191), providing a standardised approach to recording and reporting HRM measurements.

Bolus texture modification and volume regulation are regularly implemented in dysphagia management with the intention to slow bolus flow, enhance bolus control, and optimise swallow initiation and airway protection (24, 278), however, until now, the respondent swallow mechanics have not been comprehensively documented (97, 279). Additionally, in clinical practice, optimal viscosity levels for oropharyngeal dysphagia (OPD) treatment in the individual patient need to be ascertained more discriminately across dysphagia-causing aetiologies (280). Age-related changes to swallow physiology are well recognised, particularly in adults over 60 years of age (281). Gender has less impact on pharyngeal and UOS contractility (167, 209, 282), with only small effects seen for longer pharyngeal pressure duration in females (282), and there is greater pharyngeal pressure during cued effortful swallowing (167).

The effects of bolus volume (150, 156, 167, 195, 196, 244, 283), and viscosity (167, 209, 283, 284), on unimpaired swallowing biomechanics have previously been documented with high-resolution manometry. This study characterised the oropharyngeal swallow response to a wider than previously studied range of bolus volumes and consistencies using HRM with impedance (P-HRM-I). We aimed to determine which, of a recently established suite of core outcome metrics (191) and set of novel bio-mechanical measures, were most influenced by bolus condition, accounting for age and gender effects. We tested the following hypothesis: parameters indicative of distension and flow-timing would be the most responsive and therefore could, in the future, function as diagnostic markers to detect impaired swallow modulation in patients with dysphagia.

6.2 Method

6.2.1 Study Cohort

This prospective study was approved by the Southern Adelaide Clinical Human Research Ethics Committee (SAC HREC EC00188). Healthy adults were enrolled between the ages of 18 – 80 years unless they met the following exclusion criteria: previous abdominal or head & neck surgery; subject reported swallowing difficulties or symptoms of heartburn or regurgitation; uncontrolled diabetes; blood pressure abnormalities; pregnancy; allergy to local anaesthesia; and medication affecting gastrointestinal motility. Any daily medications were assessed by the study doctor (author CC) before enrolment. Dysphagia screening was conducted and produced normal scores from the DAKKAK score (285) and Sydney Swallowing Questionnaire (286). All manometry investigations were performed in the Gastroenterology & Hepatology Department at Flinders Medical Centre. In compliance with ethical requirements each participant was provided with refreshments on completion of the protocol, observed for 30 minutes and then contacted 24 hours following participation.

6.2.2 High-resolution Manometry with Impedance

An 8 French solid-state unidirectional high-resolution manometry catheter (32 pressure sensors at 1cm, 16, 2 cm length impedance segments, Unisensor/Laborie, Attikon, Switzerland) was used for data collection. Inbuilt catheter sensors detected pressures along the swallowing tract from velopharynx to proximal oesophagus. Adjacent impedance electrode segments simultaneously detected bolus contact. Following data acquisition, each de-identified pressure-impedance file was exported as an ASCII file and uploaded to the Swallow Gateway™ web-application for analysis (215).

6.2.3 Test Bolus Formulation and Swallow Protocol

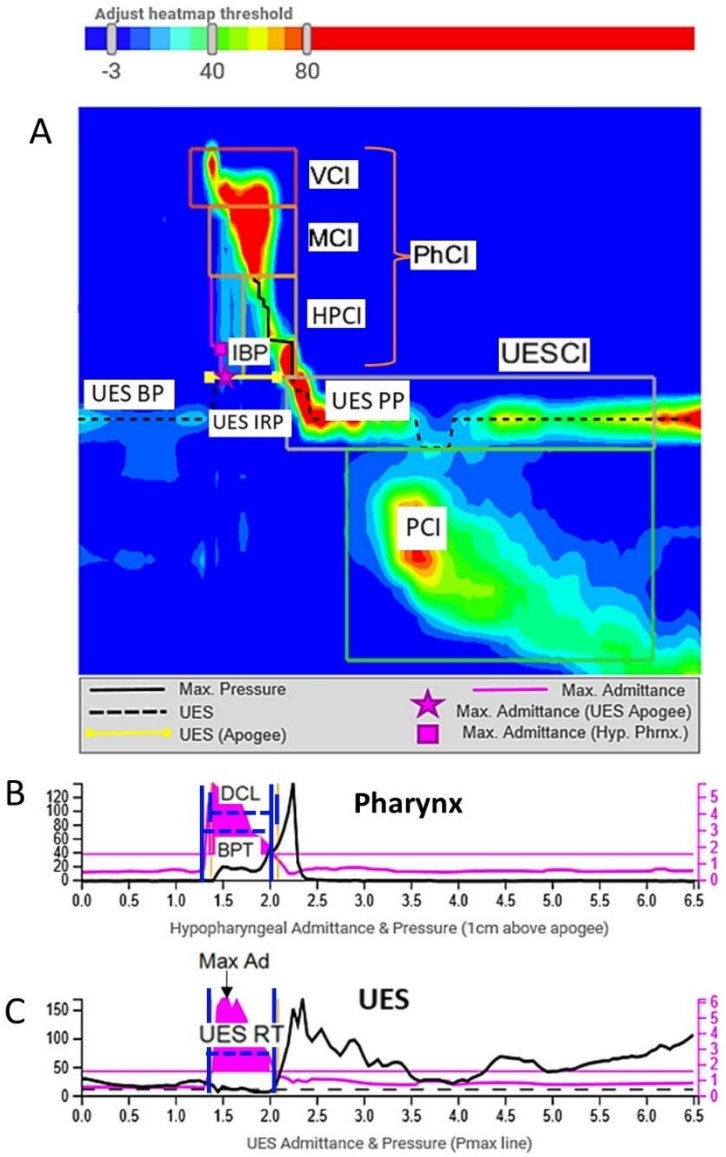
Participants were fasted for a minimum of three hours, and prior to catheter positioning Lidocaine spray (5%) was applied to one nostril. Participants were tested while seated in a head neutral, upright position. The HRPM protocol for each participant involved triplicate cued swallow challenges across 12 liquid bolus conditions (total 36 swallows) administered via syringe. The conditions comprised three consistencies (thin, mildly thick and extremely thick; see below) and four volumes (3, 5, 10 and 20ml). Prior to any bolus administration, participants were informed to attempt single swallows per bolus through the study, however, were assured that multiple swallows were not to be avoided if felt to be required. The fluid consistencies for the protocol were prepared using the Standardised Bolus Medium (SBMkit) product (Trisco Pty Ltd, Australia), purpose-formulated to optimise stable bolus electrical conductivity properties across all bolus consistencies, ensuring reliability of impedance-based measurements. The SBMkit comprises an apple flavoured, sodium chloride (NaCl) concentrate solution, and a separate gum-based thickener (Precise Thick'N Instant), which during preparation are added to tap water. The International Dysphagia Diet Standardization Initiative (IDDSI) protocols (287) were used to confirm mildly thick (IDDSI level 2 by 10 second syringe drip test) and extremely thick (IDDSI level 4 by spoon tilt test), and a HAAKE Viscotester 550TM viscometer (Thermo Electron, Karlsruhe, Germany) was used to assess the shear viscosity values of 137.37 ± 5.16

mPa·s (IDDSI 2) and 637.49 ± 33.71 mPa·s (IDDSI 4) at $50s^{-1}$ (batch number 59676), by using 10.27g and 30.83 gr in ionic solution till 200ml.

6.2.4 Swallow Gateway™ Analysis

Data were exported to the Swallow Gateway™ online application for analysis (www.swallowgateway.com; owned and provided by Flinders University, Adelaide, South Australia). Swallow analysis was conducted by the PhD candidate and cross-checked by principal supervisor. While blinded analysis would be optimal, bias is minimised by the semi-automated swallow analysis methods. Results were generated in accordance with a recommended core outcome set (191), and novel (additional to core outcome set) Swallow Gateway™-specific metrics were also derived; see Table 6.1 for a complete list of parameters and definitions. For the most part, the recommended core outcome set describes four key types of bio-mechanical phenomena: lumen occlusive pressures at the velopharynx, mesopharynx, hypopharynx, and UOS; hypopharyngeal intra-bolus pressures (IBP); UOS opening extent, and UOS relaxation. Analytic methods and reliability of Swallow Gateway™ analysis have previously been described (215). Pharyngeal swallows are selected from the manometric tracing and labelled according to bolus administration. In this study, piecemeal swallows were excluded from analysis as a reduction in bolus volume seen with piecemeal swallows is known to alter swallow biomechanics. Figure 6.1 demonstrates the selection of spatial and temporal landmarks, which define the boundaries for semi-automated analysis. Swallow parameters that have previously been correlated with pathophysiological outcomes, e.g., radiologically confirmed aspiration (59, 236, 276), are then derived.

Figure 6.1. ***Pressure Flow Parameters Indicated on a Topography Plot***



Note. Panel A: Example of a pressure topography swallow plot. Panel B: Integrated pharyngeal pressure profile and impedance/admittance curves. Panel C: Integrated UOS pressure profile and impedance/admittance curves. Abbreviated pressure flow measures incorporated in the figure to correspond with definitions in Table 6.1.

6.2.5 Statistical Analysis

The average results for each of the 12 swallow test conditions were tabulated in an Excel spreadsheet for statistical analysis using SPSS (IBM Corp. IBM Statistical Package for the Social Sciences [SPSS] Statistics for Windows, v. 25.0 Armonk, NY: IBM Corp). Data with a

skewed distribution were normalised by log transformation prior to analysis. The main effects of volume, viscosity, age and gender were evaluated using generalised linear mixed model. Bonferroni adjustment was applied to pairwise comparisons.

Table 6.1. ***P-HRM-I Pressure Flow Parameters and Definitions***

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

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

Note. This table demonstrates the core outcome set metrics and additional to core outcome set metrics, with pressure-flow subtype, measurement label with abbreviation, and definitions.

6.3 Results

Fifty healthy volunteers (mean age 46 years; age range 19-78 years old; 29 females, 21 males) were included in this study and group characteristics are outlined in Table 6.2. Participants were grouped <60 years or >60 years as age related changes in healthy swallowing have been shown to commence around 60 years of age (146, 167, 244, 283, 288). The manometry procedure was well-tolerated across the cohort. One participant had difficulties with the

catheter in situ, therefore a limited number of swallows were acquired for this subject. Piecemeal swallowing, whereby the orally administered bolus is swallowed in portions, rather than in whole, was observed for 38 swallows (6%) across 27 individuals. Results from piecemeal swallows were removed to ensure the data in this study represent single swallow bolus transfer per volume given. However, normal reference ranges of un-cued piecemeal swallowing across larger bolus volumes in future studies would have clinical utility. All results for main effects are presented in Table 6.3.

Table 6.2. ***Participant Characteristics and Metric Means per Age Group***

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

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

Table 6.3. ***Core outcome set metrics and Additional to core outcome set metrics***

CORE OUTCOME SET METRIC						
Measurement Subtype	**Measurement**	**GLMM parameters**	**Volume Effect**	**Viscosity Effect**	**Age Effect**	**Gender Effect**
Pharyngeal lumen occlusive pressure	Pharyngeal contractile integral (PhCI)	*F* *P*	↑**5.42** **0.001**	0.74 ns	2.01 ns	↑**95.24** **<0.001**
	Velopharyngeal contractile integral (VCI) *	*F* *P*	↑**9.27** **<0.001**	0.07 ns	↓**7.29** **0.007**	↑**54.87** **<0.001**
	Mesopharyngeal contractile integral (MCI) *	*F* *P*	0.46 ns	0.23 ns	↓**8.98** **0.003**	↑**181.2** **<0.001**
	Hypopharyngeal contractile integral (HPCI)	*F* *P*	↑**2.87** **0.04**	1.53 ns	0.67 ns	1.29 ns
Hypopharyngeal intra-bolus distension pressure	Hypopharyngeal intra-bolus distension pressure (IBP)	*F* *P*	↑**26.30** **<0.001**	↑**10.49** **<0.001**	↑3.36 0.07	↓**12.06** **0.001**
UOS relaxation & opening	UOS integrated relaxation pressure (UOS IRP)	*F* *P*	↑**43.47** **<0.001**	↑**35.93** **<0.001**	↑**21.71** **<0.001**	↑**9.03** **0.003**
	UOS relaxation time (UOS RT) *	*F* *P*	↑**32.87** **<0.001**	↓**9.25** **<0.001**	1.21 ns	↑**43.49** **<0.001**
	UOS maximum admittance (UOS Max Ad)	*F* *P*	↑**383.2** **<0.001**	↑**51.84** **<0.001**	↓**7.68** **0.006**	↓**19.62** **<0.001**
ADDITIONAL TO CORE OUTCOME SET SWALLOW GATEWAY™ SPECIFIC METRICS						
Measurement Subtype	**Measurement**	**GLMM parameters**	**Volume Effect**	**Viscosity Effect**	**Age Effect**	**Gender Effect**
UOS contractile measures	Upper oesophageal sphincter contractile integral (UOSCI) *	*F* *P*	↑**4.78** **0.003**	1.81 ns	1.05 ns	↑**83.73** **<0.001**
	UOS basal pressure (UOS BP) *	*F* *P*	0.33 ns	↓**10.08** **<0.001**	0.32 ns	↑**69.40** **<0.001**
	UOS peak pressure (UOS PP)	*F* *P*	↑**3.98** **0.008**	1.46 ns	↑**38.13** **<0.001**	↑**50.14** **<0.001**
Proximal oesophageal contractile measure	Proximal oesophageal contractile Integral (PCI)	*F* *P*	↑**20.13** **<0.001**	↑**7.88** **<0.001**	0.005 ns	↑**20.22** **<0.001**
Flow Timing measures	Pharyngeal Distension-Contraction Latency (DCL)	*F* *P*	↑**71.93** **<0.001**	↓**14.09** **<0.001**	2.22 ns	↑**5.35** **0.02**
	Bolus Presence Time (BPT) *	*F* *P*	↑**31.61** **<0.001**	↓**8.59** **<0.001**	0.34 ns	↑**14.00** **0.001**
Global Swallow Risk Index	Swallow Risk Index (SRI) *	*F* *P*	↑**31.71** **<0.001**	↑**3.19** **0.04**	↑**4.55** **0.03**	↓**3.98** **0.05**

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

6.3.1 Core Outcome Set Pressure Flow Parameters

6.3.1.1 Pharyngeal Lumen Occlusive Pressures: Pharyngeal, Velopharyngeal, Mesopharyngeal, and Hypopharyngeal Contractile Integrals

Lumen occlusive pressures measured as contractile integrals (CI) of the pharynx were augmented as bolus volume increased. Pairwise comparisons are displayed in Figure 6.2.A significant main effect of volume was observed for contractility at the level of velopharynx (VCI) ($F=9.27$, $p<0.001$), and hypopharynx (HPCI) ($F=2.87$, $p=0.04$); see Table 6.3. Pairwise differences between volumes were observed for VCI; see Figure 6.2.A. Viscosity did not affect pharyngeal contractility; see Table 6.3 and Figure 6.2.A. Age did not affect overall pharyngeal contractility as defined by PhCI, however, older subjects demonstrated evidence of reduced velo- and mesopharyngeal contractility ($F=7.29$, $p<0.007$, and $F=8.98$, $p=0.003$ respectively; Table 6.3). A large gender effect was seen, with male participants showing greater contractility of the pharynx overall ($F=95.24$, $p<0.001$), as well as greater velo- and mesopharyngeal contractility compared to female participants ($F=54.87$, $p<0.001$ and $F=181.2$, $p<0.001$ respectively).

6.3.1.2 Hypopharyngeal intra-bolus pressure

Hypopharyngeal intra-bolus pressures (IBP) were altered by both increased volumes and viscosity (main effects $F=26.30$, $p<0.001$, and $F=10.49$, $p<0.001$ respectively). Significant pairwise differences were observed across all volume combinations with greater IBP observed with larger volumes ($p<0.005$) and viscosity combinations (IDDSI level 0 vs. level 2 $p=0.03$, vs. level 4 $p<0.001$, and level 2 vs. level 4 $p<0.05$); see Figure 6.2.D. Older subjects showed a

trend towards higher IBP values (F=3.36, p=0.07), while male subjects demonstrated overall lower IBP values compared to females (F=12.06 p=0.001).

6.3.1.3 UOS relaxation pressure

Like IBP, UOS integrated relaxation pressures (UOS IRP) demonstrated significant main effects seen with increased UOS IRP observed for increased volume and viscosity (F=43.47, p<0.001 and F=35.93, p<0.001, respectively). Significant pairwise differences are depicted in Figure 6.2.D. UOS IRP increased with age (F=21.71, p<0.001), and, in contrast to the IBP, was higher in male vs female subjects (F=9.03, p =0.003).

6.3.1.4 UOS relaxation duration and opening extent: UOS max. admittance, UOS relaxation time

UOS relaxation time increased with higher bolus volume swallows (main effect F=32.87, p<0.001; see Figure 6.2. for pairwise comparisons) but was reduced during heavier viscosity swallows (F=9.25, p<0.001). UOS opening, as measured using UOS maximum admittance (UOS max ad), revealed the most sensitive findings across this study based on the size of main effect and number of pairwise differences. Both volume and viscosity increase the UOS max ad (F=383.2, p<0.001 and F=51.84, p<0.001 respectively; pairwise comparisons are shown in Figure 6.2.D).

6.3.2 Additional Pressure Flow Parameters

6.3.2.1 UOS Contractile Pressures: UOS Basal Pressure, UOSCI, UOS Peak Pressure and Proximal Oesophageal Contractile Integral

A small numerical increase in pre-swallow UOS basal pressure was seen with larger bolus volumes, however this did not reach significance; see Figure 6.2.C. In contrast, bolus viscosity had a significant main effect in reducing UOS basal pressure (F=10.08, p<0.001), with pairwise significance for 10ml volumes only IDDSI level 0 vs. level 2; p=0.05, level 4, p=0.02; see Figure

6.2.C. A significant increase in post-swallow activity of the UOS was observed with larger bolus sizes as demonstrated based on a higher UOS contractile integral (UOSCI) (main effect F=4.78, p=0.003), and UOS peak pressure (main effect F=3.98, p=0.008). Pairwise differences between volumes were observed for UOSCI nor UOS peak pressure; see Figure 6.2.B. Viscosity affected neither UOSCI, nor UOS peak pressure.

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

The activity of the proximal oesophagus was highly responsive to bolus conditions, with proximal oesophageal contractile integral (PCI) increasing with both volume (main effect F=20.13, p<0.001) and viscosity (main effect F=7.88, p<0.001); see Figure 6.2.B. Age had no effect on PCI, however male subjects had significantly increased PCI measurements compared to female participants (F=20.22, p<0.001).

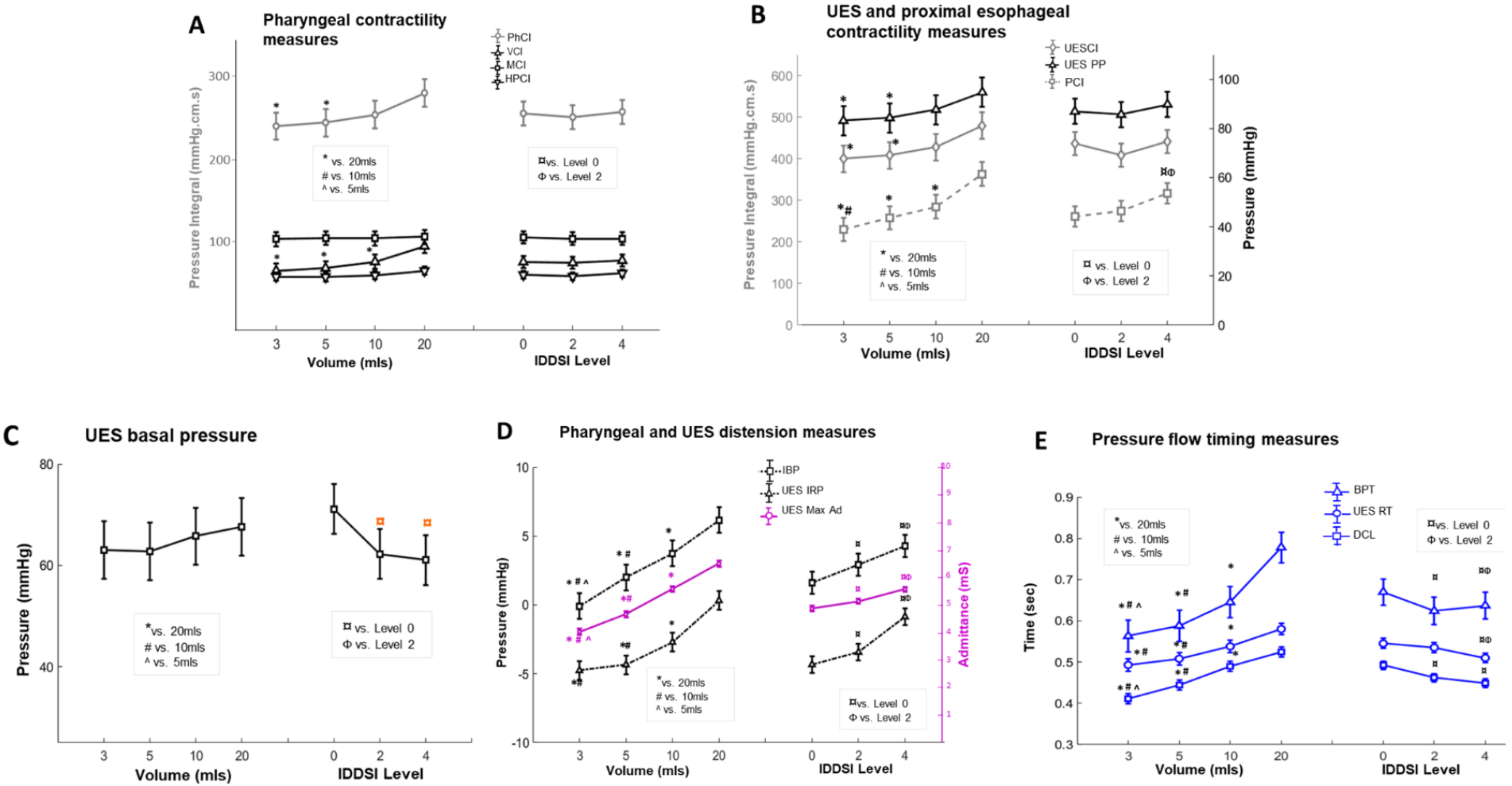
6.3.2.2 Pharyngeal Flow Timing and Bolus Presence: DCL and BPT

There were significant main effects of volume and viscosity on timing variables. Distension to contraction latency (DCL) and bolus presence time (BPT) were lengthened by volume (F=71.93, p<0.001 and F=31.61, p<0.001 respectively) and were shortened by viscosity (F=14.09, p<0.001 and F=8.59, p<0.001); see Figure 6.2.E. Age had no effect on DCL and BPT, but a significant gender effect (F=5.35, p=0.02 and F=14.00, p<0.001) was observed with male participants showing increased DCL compared to females.

6.3.2.3 Swallow Risk Index: SRI

Swallow Risk Index, a global composite score designed to capitalise on the directionality of aberrant swallow parameters, increased as bolus volume and viscosity increased (main effects F=31.71, p<0.001 and F=3.19, p=0.04 respectively). The SRI increased in older age groups (F=4.55, p=0.03) and was reduced in males (F=3.98, p=0.05).

Figure 6.2. ***Effects of bolus volume and viscosity***



Note. Graphs showing effects of volume and viscosity for A: pharyngeal contractility measures; B: UOS contractility measures, and proximal oesophageal contractility; C: UOS Basal pressure; D: pharyngeal and UOS distension measures; and E: Pressure flow Timing measures. ***** depicts Bonferroni adjusted pairwise significance vs. 20ml volumes; # vs. 10mls and **^** vs. 5mls. ¤ depicts Bonferroni adjusted pairwise significance vs. IDDSI level 0; **Φ** vs. IDDSI level. Graphs are presented with American spelling as produced for publication.

6.4 Discussion

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

6.4.1 Pharyngeal, UOS and Proximal Oesophageal Contractility Measures

With increasing bolus volumes, we observed modulatory responses to pharyngeal contractility. The largest increases were seen in the velo-pharyngeal contractile integral (VCI), reflecting pressures that seal the pharyngeal chamber proximally, which is in line with previous research (167, 244, 283). The observed change in contractility indicates greater force generation as a larger bolus volume is propelled. UOS post swallow pressures also increased with increasing bolus volumes, and it has been suggested that this contraction helps to prevent retrograde bolus return immediately post swallow (289). Of interest, increased bolus viscosity had little or no effect on the VCI or any other pharyngeal contractility measurements. This is in line with some previous work (167, 283), while others have reported reduced pharyngeal contractility, measured as maximum pressure values, with increased viscosity (284). In relation to the hypopharynx specifically, the current study detected a small overall increase in hypopharyngeal

contractility with increasing volume, and increased hypopharyngeal IBP was also observed. This contradicts previous research (196), which reports these pressures are not dependent on bolus volume. However, we propose our larger sample size in this current study may have revealed subtle pharyngeal contractility changes not noted by previous research.

Overall, our findings have demonstrated a more pronounced stimulus from bolus volume, compared to bolus viscosity for modulation of the pharyngeal swallowing motor program. However, interestingly, the pre-relaxation UOS basal pressure was significantly augmented for thinner bolus consistencies, an effect that was most pronounced at 10ml volumes, and while this is not widely documented it corresponds with another recent report (284). This may suggest an anticipatory activation of the UOS during the earliest phases of the swallow motor response i.e. in concert with earlier onset of hyolaryngeal excursion and earlier CP muscle relaxation that occur to accommodate thinner fluids, which arrive earlier at the airway opening (195). Furthermore, an element of UOS volitional control has recently been shown, whereby healthy volunteers were trained with manometric biofeedback to elevate or reduce UOS pressure (290). This suggests that pre-swallow UOS basal pressure may be influenced by preparatory central and possible volitional factors. In general, the UOS pre-swallow contraction is thought to assist in the creation of negative pressures within the proximal oesophagus which, upon UOS opening, causes a bolus suction effect that facilitates bolus transfer into the oesophagus (197, 211, 218). This suction effect is associated with negative nadir UOS relaxation pressures, a biomechanical feature which was apparent in our participants, particularly during smaller volume swallows.

Observations in relation to proximal peristalsis of the oesophageal body are not widely reported in the literature when compared to the pharynx and distal oesophagus. However, in the current study, we observed marked effects of bolus condition on proximal oesophageal contractility. Indeed, the proximal oesophageal contractile integral (PCI) was by far the most responsive of all reported contractile measures, increasing significantly with both liquid volume size and viscosity level. Experimental luminal fluid distention of the oesophagus in isolation is well

known to initiate secondary peristalsis as well as a range of other specific oesophageal and UOS contractile reflexes governed by central and enteric nervous system circuits (209, 224, 244, 283, 291). Activation of some mechanoreceptor-initiated peripheral circuits is also likely to occur during volitional bolus swallowing. Their effects are potentially superimposed leading to alteration of the esophageal contractile response. Our data show that the fluid bolus conditions that generated the highest lumen distension pressures during bolus transport were associated with the greatest level of proximal oesophageal contractile response. Importantly, the broad-based responsiveness of the proximal oesophagus to physiological bolus distensions differed to the pharyngeal regions which only showed volume-related increases in contractility, despite viscosity level also being a potent driver for distension pressure, as is described below.

6.4.2 Pharyngeal and UOS Distension Measures

Using a variety of acquisition methods, measurements and swallow protocols, previous research has established that larger bolus volumes are associated with higher pharyngeal distension pressures and longer UOS opening to accommodate earlier arrival of the bolus (209, 224, 244, 283). Results from this study highlight three metrics (each relating to the proficiency of UOS relaxation and opening), which responded significantly to increases in volume and viscosity. These were: i) hypopharyngeal intra-bolus pressure (IBP), ii) UOS maximum admittance, and iii) UOS integrated relaxation pressure (IRP). Age and gender effects in this study also confirm their sensitivity for detecting subtle changes within an otherwise normally functioning system (167, 205). Our results suggest these metrics are key markers of swallow modulation.

Elevated hypopharyngeal intra-bolus pressure is known to flag possible UOS outflow obstruction in patients as upstream hypopharyngeal pressures elevate with increased viscosity, increased trans-sphincteric bolus flow rate, reduced UOS aperture, and/or reduced hypopharyngeal and/or UOS distensibility (172, 173, 197). The observed effects of age and

gender possibly indicate a subtle reduction in compensatory reserve in older individuals, and possibly larger pharyngeal chambers overall in males able to accommodate the bolus challenges with less impact on IBP compared to female participants. Understanding normal IBP modulation may assist in assessment and interpretation of difficult dysphagia cases with and without obvious features of UOS dysfunction.

UOS maximum admittance, a marker of UOS opening extent (249), detected differences at all volume increments across all viscosity levels. This was the only metric able to distinguish between 3ml and 5ml volumes for both thin and mildly thickened fluids. Maximum admittance has previously been described as a non-specific marker of reduced UOS opening (249), with low admittance values flagging impaired bolus driving forces and/or UOS luminal restriction. Additionally, the UOS pressures during relaxation and reception of the propelled bolus (UOS IRP) were progressively elevated as the volume and viscosity increased, as has previously been shown with high resolution manometry (167). With significant pairwise comparisons between lower and higher volumes and consistencies, and differences for age and gender, the sensitive alterations of UOS opening and relaxation pressures demonstrate the potential for these measures to be used to detect not only overt but also subtle swallow modulation dysfunction.

6.4.3 Flow Timing Measures

The current study shows that distension, relaxation and contractility timing are key physiological features of the pharyngeal swallow response that are substantially altered in relation to bolus conditions. This is perhaps not surprising as the optimal timing and coordination of bolus arrival with luminal opening and closure serves to minimise resistance to bolus flow and optimise airway protection in a healthy swallow system (196, 225). The components of UOS opening, achieved by hyolaryngeal excursion, bolus propulsive forces and CP muscle deactivation are all thought to be influenced by bolus volume, and modified via central pattern modulation in the brainstem (224). In this study, UOS relaxation time increased with larger bolus volume as has been shown in previous work (292), whereas increasing bolus

viscosity decreased UOS relaxation time in our study. It is likely that faster moving boluses, as seen with larger volumes and thinner bolus types, are associated with an earlier onset of UOS relaxation when compared to a heavier and slower bolus (197); this has previously been shown in smaller volumes (284). In contrast to our current findings, a recent radiological study of a <60yr old cohort reported no effect of viscosity on UOS opening duration. However, they showed swallow reaction time was significantly later with thicker bolus types (97), and time to laryngeal vestibule closure was shorter, both relative to a later hyoid elevation movement and a prompter airway protective response once the hyoid movement commenced (97).

Pharyngeal distension is influenced by lingual propulsion, which facilitates timely arrival of a cohesive bolus ahead of the pharyngeal stripping wave. Timing between pharyngeal distension and contractility (DCL), and overall BPT in the pharynx, revealed similar results to UOS relaxation time. Longer durations of DCL and BPT were seen in response to larger volumes, however durations were shorter in response to increased viscosity. This can be explained by the relatively later arrival of a thicker bolus into the pharyngeal chamber compared to a thin fluid, which flows faster and therefore arrives comparatively ‘earlier’ in the swallow sequence in relation to the pharyngeal contraction, which is largely stereotypical in its timing. Overall, this study demonstrates flow-timing metrics which are sensitive to volume changes and discriminated all increments for each separate viscosity level. All timing metrics are therefore potentially useful clinical markers of aberrant swallow modulation and potentially useful markers of swallow improvement when fluid viscosity is modified.

6.4.4 Swallow Risk Index

Finally, the SRI increased with volume, viscosity, age, and gender. The SRI has previously proven useful in dysphagia assessment and has been proposed as a global marker of swallow dysfunction (59, 249, 250, 276, 281). Our study supports this concept, showing that the SRI has sufficient sensitivity to detect bolus condition changes. The SRI increase, albeit within normal limits, seen with increased viscosity is driven by a correlated increase in IBP and a

reduced DCL measure with more viscous boluses. These two individual metrics are responding as we would expect to increased viscosity, however, their contribution within the SRI formula amplifies the index comparative to thin fluid swallows. In patients with evidence of pre-swallow pharyngeal bolus presence, the SRI decreases with viscosity (247). Together with the subtle alterations related to age and gender effects, our findings suggest an abnormal SRI may be a useful global measure to detect inadequate swallow modulation.

6.4.5 Limitations

This study is limited in that measurements undertaken using P-HRM-I were not directly correlated with videofluoroscopy, as radiation exposure, ethically, could not be justified. We note that several previous manometry studies have reported and validated the physiological measures against radiological outcomes in both healthy controls and patients with dysphagia, albeit with varying acquisition methods and protocols (140, 172, 211, 236). Unidirectional pressure sensors along the catheter assembly may have produced variability within pressure readings, therefore confirmation of these study findings with circumferential pressure sensor techniques will be valuable in future studies. Bolus volumes and viscosity challenges in our study were undertaken in a fixed order, rather than a randomised protocol. Therefore, data may be subject to time and order effects. With this extensive protocol, which spanned up to 30 minutes, sensory accommodation may have influenced the results. Our findings must be interpreted in relation to known viscosity-based rheological constructs. We have provided standardised measurements with gum based thickening agent bolus preparations tailored to the IDDSI recommendations, which can vary greatly within each broad IDDSI-based viscosity level, particularly between gum vs. starch based thickening agents (97, 293, 294). However, in this study the gum-based bolus media underwent rheological testing at the IDDSI specified viscosities. We have included these data for completeness and translatability. Future P-HRM-I studies could explore differences between gum and starch based thickening agents, and

precise bolus rheological characteristics such as elasticity, adhesiveness, cohesiveness (280) and shear thinning qualities (295, 296), which may influence swallow biomechanics.

Strengths of the study were a sample size permitting adequately powered statistical analysis, and balance for age and gender effects. This study adds to the current literature a comprehensive report of healthy swallow modulation relating to a range of bolus volume and viscosity conditions not previously reported. A set of normative values can now be referenced within clinical practice. The use of www.swallowgateway.com software, now generalised for routine use to derive consensus-recommended, as well as novel analytics, enables further investigations across centres and study cohorts to both confirm and extend our findings. Beyond the effects of texture modification and volume regulation, neuro-stimulants are increasingly under investigation for their use as OPD treatments (261, 297) and future studies could explore the biomechanical implications with P-HRM-I methods.

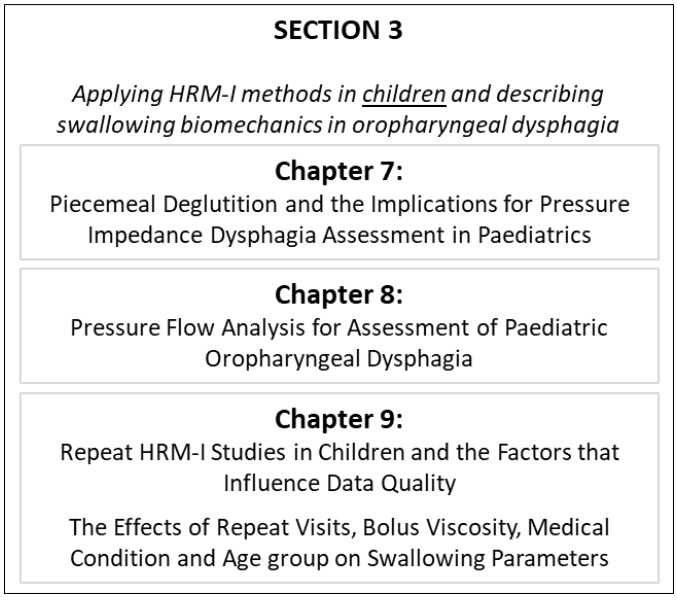
6.5 Conclusion

Describing swallow modulatory effects comprehensively in healthy participants, with a core outcome set and a unified analysis system, represents a further step towards optimising diagnostic frameworks for oropharyngeal dysphagia. We report key swallowing modulation measures in response to a thorough set of volume and viscosity ranges using standardised and experimental P-HRM-I parameters. Some findings of this study were confirmatory of established knowledge, however other subtle and key differences not previously documented are highlighted and present as important biomechanical indicators of healthy swallow modulation. From the recommended core outcome set (191) hypopharyngeal intra-bolus pressure, UOS maximum admittance, UOS relaxation pressure and UOS relaxation time altered most significantly with bolus condition. Further exploration in dysphagia patients will substantiate these results and determine the clinical value of these measures, which have previously been difficult to achieve.

This concludes Section 2, which has demonstrated that healthy adult pharyngeal swallowing can be characterised in detail with P-HRM-I measurements. In particular, healthy swallowing neuromodulation to bolus volumes and viscosities was shown. Section 3 outlines the application of P-HRM-I techniques in children in Chapters 7 to 9, commencing with the exploration of the impact of PD on P-HRM-I pressure flow parameters.

SECTION 3

The studies in Section 2 established the biomechanical features we can expect to see when swallowing neuromodulation is intact. Both healthy adult studies in Section 2 represent single swallowing of boluses, however approximately 6% of the total swallows were excluded from the data due to piecemeal swallowing of larger bolus volumes. Research Section 3 includes three paediatric P-HRM-I studies guided by research questions detailed in sections 3.1.3, 3.1.4 and 3.1.5. In recognising that piecemeal deglutition is a common swallowing feature, particularly in paediatric patients with dysphagia, the following chapter explores the impact of piecemeal deglutition on P-HRM-I recordings and details a method for selecting swallows for analysis, guided by impedance curves. Chapter 8 describes P-HRM-I pressure flow parameters observed in children with clinical signs of OPD. Chapter 9 explores the factors influencing repeat testing, data quality, and highlights P-HRM-I parameters according to visit, bolus viscosity, medical condition and age group of the paediatric cohort studied.



Chapter 7: Piecemeal Deglutition and the Implications for Pressure Impedance Dysphagia Assessment in Paediatrics

I am first author of this chapter, now published[7]. I declare that I was principally responsible for writing the manuscript submitted for publication. I recruited all participants, acquired all high-resolution impedance manometry studies (P-HRM-I) and completed all data analysis. I was assisted by author Taher Omari with statistical analysis and interpretation of the findings. Please see the form in Appendix 8 with the statement of contribution from all co-authors of this chapter.

[7] Text in this chapter has been published as:

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7.1 Introduction

Pharyngeal high-resolution impedance manometry (P-HRM-I) provides objective pressure and integrated bolus flow assessment of paediatric swallowing (54, 207, 298). To date, analysis of P-HRM-I assessments has relied on selection of the primary swallow following oral administration of a bolus, even when a bolus is swallowed in multiple portions. Piecemeal deglutition (PD), defined as swallowing of one single bolus in two or more portions in order to empty the oral cavity (24), is a common feature of paediatric swallowing. Whilst paediatric PD research in infants >6months is limited, it is expected that PD occurs normally when the swallow mechanism is challenged with a larger than optimal bolus volume (259); however, in OPD, PD may even occur for boluses of optimal volume and is, therefore, suggestive of impairment (299, 300).

The healthy swallowing mechanism modulates to accommodate bolus volumes, and this is reflected by changes to pressure flow metrics detected from P-HRM-I methods. Incremental increases in volume have shown larger velopharyngeal to tongue base occlusive pressures for propulsion of a bigger bolus; higher hypopharyngeal intra-bolus pressure (hIBP); earlier upper oesophageal sphincter (UOS) relaxation; and earlier and wider UOS opening (195, 196, 225, 244, 262). Therefore, as PD naturally distributes the administered volume over several piecemeal swallows, it follows that pressure flow swallow metrics will in turn be altered.

Manometry can be performed in infants and young children and enables clear observation of oropharyngeal swallowing motor patterns (54, 207, 219, 221, 298, 301). It is critical for assessors to differentiate saliva from bolus containing swallows when selecting for analysis, as only bolus swallows will allow accurate assessment of a child's ability to manage foods and liquids. This can be achieved using impedance measures that capture bolus flow (59), thus avoiding the constraints inherent with use of ionizing radiation (29). Therefore, this exploratory study aimed to: i) define a swallow selection methodology that best captures pharyngeal and UOS function in infants and children aged 5 months-4 years where PD is a feature of the P-HRM-I recording; ii) characterise PD patterns in relation to age; and iii) determine the effect of

PD patterns on swallow function variables. We hypothesised that single swallow selection (the first swallow in a piecemeal sequence) may incorrectly represent a child's bolus swallow function measures.

7.2 Methods

All investigations were performed in the Department of Paediatric Surgery at The Royal Children's Hospital, Melbourne, Australia. The institutional Human Research Ethics Committee approved the study protocol in accordance with the Australian Paediatric Research Ethics and Governance Network (HREC 35089A). Informed consent was obtained from all participants' primary caregivers prior to commencing measurements. Participants underwent investigations in the presence of a research nurse, parent/s, paediatric surgeon, and scientist/speech pathologist. The P-HRM-I recordings from each child were retrospectively analysed for the purpose of this study.

7.2.1 Cohort Characteristics

P-HRM-I procedures had been previously performed as part of a research study primarily aimed at investigating oesophageal motility in children with type IIIb oesophageal atresia (OA). In these patients pharyngeal swallowing was considered 'asymptomatic' on clinical grounds (no history of clinical symptoms, assessment or interventions for OPD). Pre-operatively, the majority of patients underwent laryngo-tracheo-bronchoscopy (LTB) to document vocal fold mobility, confirm the presence and position of the trachea-oesophageal fistula associated with this type of OA, and to exclude laryngeal cleft. In those patients that do not undergo pre-operative LTB, it is routine care at this centre for an investigation to be arranged post-operatively if patients demonstrate respiratory symptoms. None of our cohort had laryngeal cleft, vocal fold paralysis or demonstrated symptoms to warrant LTB post operatively.

For the purpose of our analysis, the participants were grouped by age: Group 1 (5 to 11 months of age) and Group 2 (1 to 4 years of age), as one year of age optimally defined developmental transition from infant to child swallowing behaviours (26, 51).

7.2.2 Measurement Protocol

The P-HRM-I recordings were acquired using an 8 French high-resolution, solid-state catheter incorporating 32 pressure sensors and 16 adjoining impedance segments (32P16Z) (Unisensor AG catheter, Attikon, Switzerland). The pressure sensors detect the sequence of pressure changes associated with swallow musculature contractions and the impedance electrodes record flow of ingested food/fluid.

The catheter was positioned trans-nasally, straddling the entire pharyngo-oesophageal segment. Where tolerated, lignocaine spray (5%) had been applied to the entrance of the nose and a water-based lubricant was used to assist with catheter placement. The pressure-impedance data were acquired at 20 samples/sec (Solar GI acquisition unit Medical Measurement Systems, Enschede, The Netherlands).

Boluses of 0.9% sodium chloride (saline) were used during the P-HRM-I assessment. These boluses had been administered orally via a syringe and a consistent volume was given to each patient, ranging from 2ml to 5ml depending on patient age/size. The manometric ‘composite pharyngeal responses’ (221) within a 15 second window were observed to define piecemeal patterns. This study presents integrated impedance with manometry data; see Figure 7.1, which demonstrates piecemeal swallowing patterns A-C, following administration of single boluses, 2-5ml. An additional panel D shows a suckle burst during continuous bottle drinking to demonstrate potential clinical application of the P-HRM-I recording. Continuous bottle drinking was not included in the study protocol; panel D is presented for clinical interest only.

7.2.3 Analysis of Pressure-Impedance Recordings

The P-HRM-I recordings were retrospectively analysed using the software platform AIMplot (copyright T Omari), which is accessible online via a web-based portal called Swallow Gateway™; see Figure 7.2. The entire P-HRM-I study was exported as an ASCII file which was then uploaded onto the website (swallowgateway.com). The impedance values are automatically transformed to their inverse product, *admittance* (admittance = 1/ohms; units in millisiemens, mS), providing a measure of bolus passage through the pharyngo-oesophageal segment.

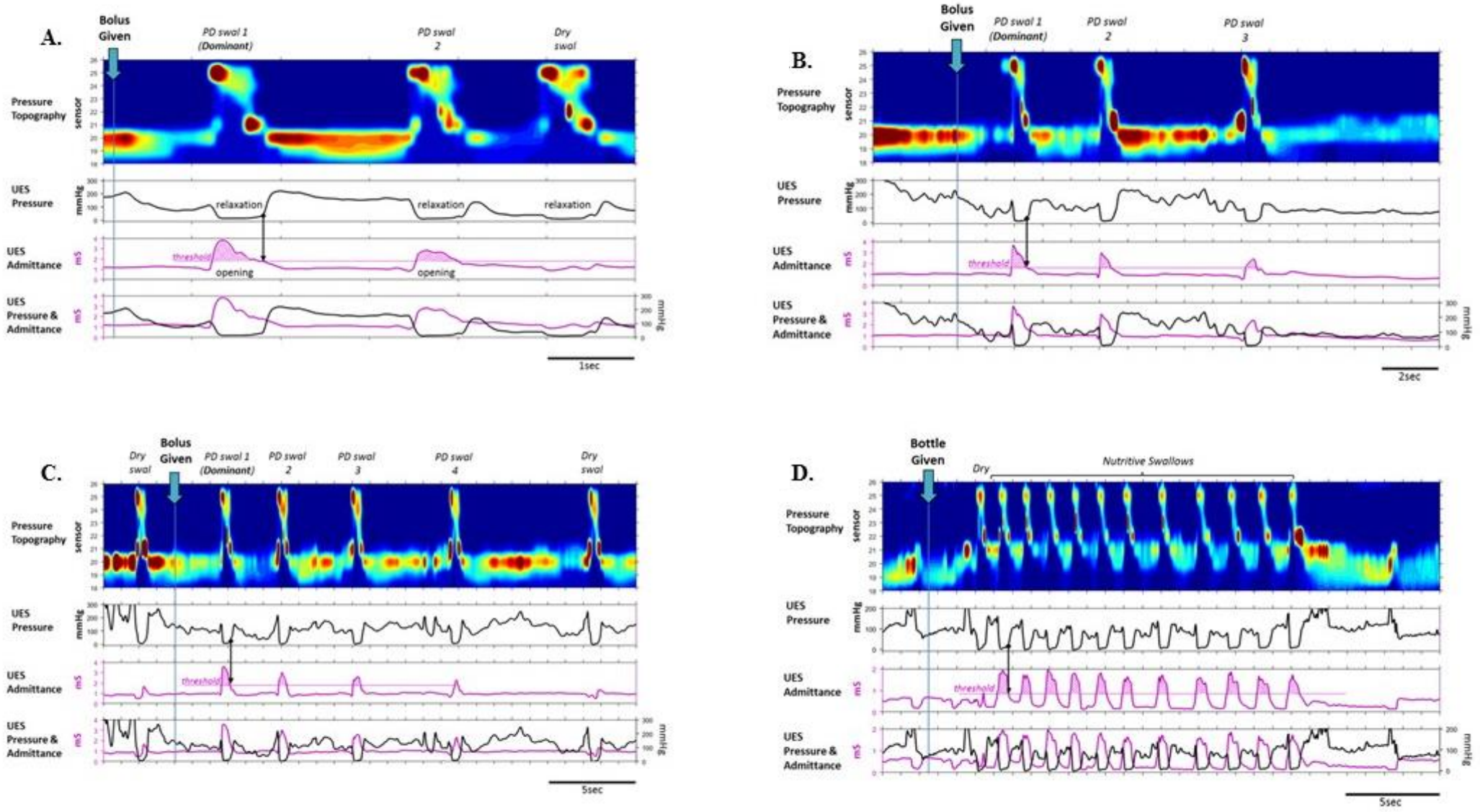
Once uploaded to Swallow Gateway™ the study was navigated in order to select pharyngeal swallow sequences (up to a maximum of 5 swallows within a 15 second P-HRM-I recording window) following bolus administration. *Piecemeal deglutition* (PD) was noted to define the swallow sequences. The largest admittance peak within the sequence specified the largest volume swallow, defined as the *dominant swallow*; see Figure 7.1. The dominant swallow was used to set the admittance threshold at the reference point of UOS closure (as defined by the onset of post-relaxation contraction of the UOS); see Figure 7.2.C. Setting the admittance threshold at UOS closure ensured that admittance values at and above this threshold were meaningful for that individual's (optimally conductive) bolus swallows. Consequently, admittance values above the threshold indicated true bolus passage with the assumption that bolus passage ceased by the time the UOS had closed. Swallows with admittance values below this threshold were considered dry/secretion swallows which were excluded from PD analysis.

Piecemeal deglutition patterns were defined according to the number of PD swallows in a sequence as follows: pattern A = 1-2 swallows; pattern B = 3 swallows; pattern C = 4-5 swallows. This definition allowed for homogenous group sizes for overall statistical comparison.

The bolus swallows in each PD sequence were individually selected and analysed to derive swallow function variables that were *averaged* for each PD sequence. Additionally, the *dominant* swallow (as defined above) was highlighted so that it could be compared to the

averaged data from each PD sequence. The swallow function variables calculated are described below.

Figure 7.1. ***Piecemeal deglutition swallowing patterns (1A-C) and a suckle burst (1D)***



Note. This figure demonstrates piecemeal deglutition swallow patterns (A - C) from a 2-year-old male, as indicated on his P-HRM-I recording. **A.** Piecemeal deglutition (PD) pattern A, 3ml saline offered, with 2 piecemeal swallows and 1 dry/secretion swallow. **B.** Piecemeal deglutition (PD) pattern B, 3ml saline offered with 3 piecemeal swallows. **C.** Piecemeal deglutition (PD) pattern C, 3ml saline offered with 4 piecemeal swallows and 1 dry/secretion swallow. **D.** To demonstrate clinical application, suckle burst during bottle feeding with 12 nutritive swallows. The regular admittance curves suggest relatively even bolus volume per swallow. Each example shows the P-HRM-I recording, followed by the upper oesophageal sphincter (UOS) pressure curves, and UOS admittance (inverse of impedance) curves. The black arrow across the second and third panel indicates UOS closure which sets the admittance threshold (horizontal pink line in panel 3). The fourth panel shows the relationship between UOS pressure activity and bolus flow. Graphs are presented with American spelling as produced for publication.

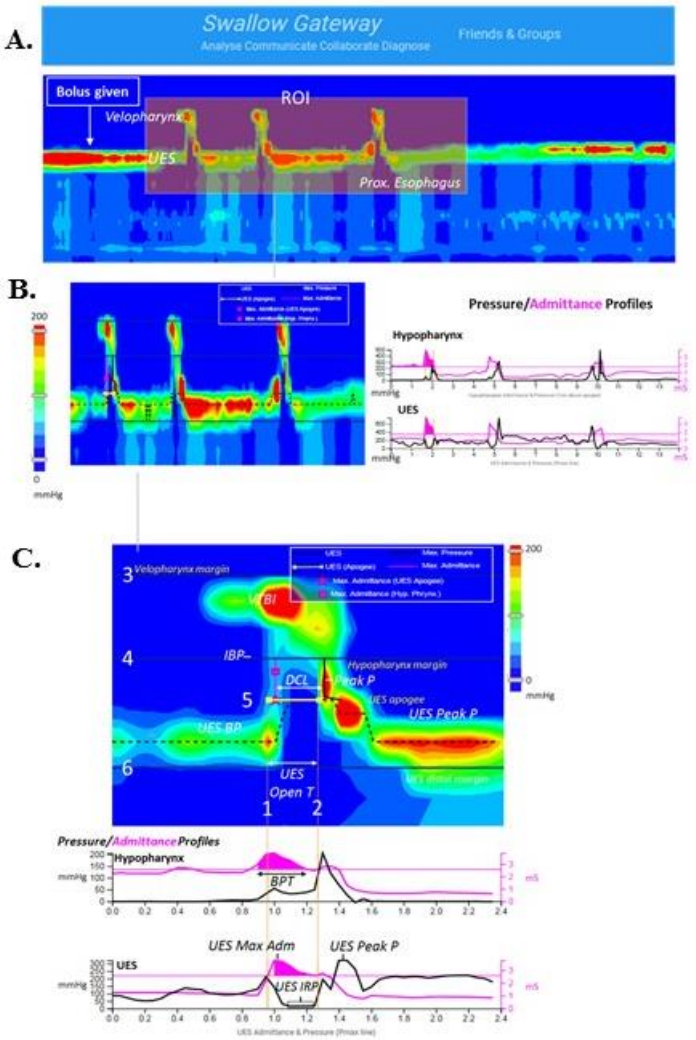
7.2.4 Swallow Function Variables

All swallow function variables (SFV) are indicated in Figure 7.2. The *velopharyngeal tongue base contractile integral* (VCI) was based on the integral of pressures within the region of the velopharynx and tongue base during a swallow. Contractility of the pharyngeal stripping wave proximal to the UOS was calculated as the *pharyngeal peak pressure* (Peak P), defined as the maximum contraction of the pharynx. Additionally, the *UOS post relaxation peak pressure* (UOS Peak P) was determined by the maximal peak pressure up to 1 second after relaxation offset. *The distension-contraction latency of the whole pharynx* (Ph DCL) was determined for the pharyngeal region proximal to the UOS apogee position. This temporal metric defines the latency from maximum bolus distension to maximal pharyngeal contraction and is a marker of how well the bolus is propelled ahead of the pharyngeal stripping wave.

The maximum admittance estimates the area at the axial centre, or most distended part, of the lumen during bolus transport (59). Hence, pharyngeal pressure measured at, and the relative timing of, maximum admittance provides an accurate measure of pharyngeal intra-bolus distension and timing of maximum distension, respectively. For this study, the hypopharyngeal intra-bolus pressure at maximum admittance, 1 cm above the UOS, was used to define *hIBP*. The maximum luminal cross-sectional area within the UOS, during bolus flow, was inferred based on the *UOS maximum admittance* (UOS Max Ad) (59, 249).

The *UOS basal pressure* (UOS basal P) and UOS relaxation pressure were determined using the *e-sleeve* method, based on the value and location of maximum axial UOS pressure over time (145). The *UOS integrated relaxation pressure* (UOS IRP) was defined as the median of all lowest pressures (contiguous or non-contiguous) recorded over a 0.25 sec period. The *UOS open time* (UOS OT) was defined by the period between the upstroke and down stroke inflexions of the UOS admittance curve.

Figure 7.2. ***Pressure Flow Analysis with AIMplot software***



Note. Swallow Function Variables derived using Pressure-Flow Analysis with AIM*plot* software via the *Swallow Gateway*™ website. **A.** The P-HRM-I recording as it appears in *Swallow Gateway*™. The PD swallow sequence is selected with a region of interest (ROI) box from velopharynx to oesophageal transition zone. **B.** The pressure/admittance profiles for Hypopharynx and UOS indicate bolus swallows, as shown by the pink shaded admittance integral. **C.** Once bolus swallows are identified, individual swallow analysis takes place with manual placement of 6 landmarks: 1) UOS opening point (first vertical yellow line); 2) UOS closure point (second vertical yellow line); 3) velopharyngeal proximal margin; 4) hypopharyngeal proximal margin; 5) UOS apogee and 6) UOS distal margin. Swallow function variables are automatically generated. This figure is presented with American spelling as produced by Swallow Gateway™.

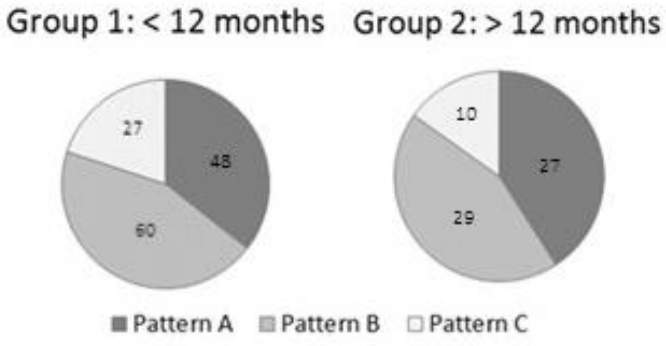
7.2.5 Statistical Analysis

The data were investigated using SPSS (IBM Corp. released 2013, IBM Statistical Package for the Social Sciences [SPSS] Statistics for Windows, v. 22.0 Armonk, NY: IBM Corp). Measurements were predominantly nonparametric, therefore for all PD pattern comparisons Independent Sample Kruskall Wallis Tests were conducted. A Bonferroni adjustment was manually applied for multiple pairwise comparisons. For age group comparisons, a Mann Whitney U Test was performed. Throughout, a p-value <0.05 indicated statistical significance.

7.3 Results

Participants who took at least 3 swallows of a constant volume of at least 2ml liquid were included for analysis. A total of 27 patients (19 males, 8 females) were included in this study. There were 13 patients in age Group 1 (median age 7 months, range 5-11 months) and 14 patients in age Group 2 (median age 18.5 months, range 13-41 months). All participants were receiving full oral diet without modification, with no clinical signs, symptoms, or history of OPD. Overall, the prevailing PD pattern was pattern B (43.7%) followed by pattern A (35.6%), and pattern C (20.7%). Group 1 (infants) and Group 2 (children 1 - 4 years) showed a similar distribution of PD patterns; see Figure 7.3. However, there were clear biomechanical differences between the age groups, consistent with a larger oral and pharyngeal chamber in the older children; see Figure 7.4.

Figure 7.3. ***Distribution of piecemeal deglutition pattern types***



Note. This figure demonstrates the distribution of PD pattern type amongst all swallow sequences. Pattern A = 1-2 swallows; Pattern B = 3 swallows; Pattern C = 4-5 swallows. Comparison of PD pattern distribution of Group 1 versus Group 2. Pearson Chi square, two-sided asymptotic significance p=0.346.

Similar findings were noted when data based on the *dominant swallow* within the PD pattern type were compared with those from the *average of the swallows*. However, the dominant swallow data showed the greatest statistical confidences for age and PD pattern main effects and are therefore presented here; see Figure 7.4, and Table 7.1.

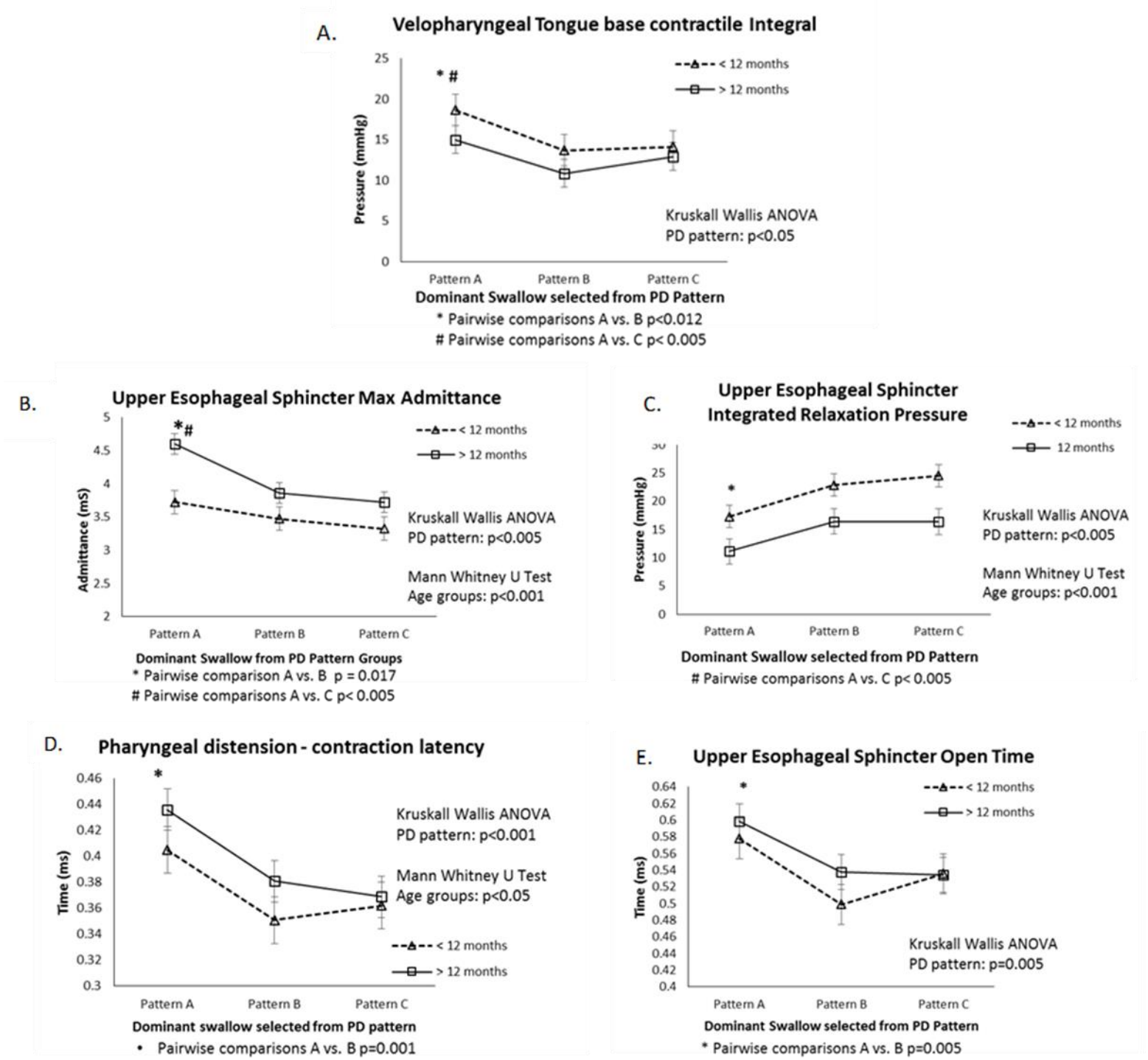
The main age-related differences were greater UOS distension diameter indicated by UOS maximal admittance; see Figure 7.1.B, and lower UOS relaxation pressures; see Figure 7.4.C, a longer distension-contraction latency; see Figure 7.4.D, and higher hIBP; see Table 7.1, amongst older children. Velopharyngeal to tongue base contractility pressures, hypopharyngeal peak pressure and UOS basal and post-relaxation peak pressure were not affected by age group; see Table 7.1. The main differences for PD pattern type were a higher velopharyngeal contractility; see Figure 7.4.A, wider UOS distension diameter indicated by UOS maximal admittance; see Figure 7.4.B, longer UOS opening time; see Figure 7.4.E, lower UOS relaxation pressures; see Figure 7.4.C, and longer pharyngeal distension-contraction latency; see Figure 7.4.D, for fewer swallows in a PD sequence. The hIBP, hypopharyngeal peak pressure, and UOS basal and peak pressures were not affected by PD pattern; see Table 7.1.

Table 7.1. ***The Effects of Piecemeal deglutition and Age Group***

	Effect of Age Group			Effect of PD Pattern	
Variable	**< 12 months**	**> 12 months**	**P-value**	**Mean Rank [0.95 CI]**	**P-value**
h IBP	59.90	76.47	***0.014***	↓ 12.50 [-23.00, 62.80]	ns
Peak P	73.70	62.05	0.084	↓ 212.38 [53.85, 621.63]	ns
UOS BP	62.58	73.67	ns	↓ 117.23 [23.77, 643.73]	ns
UOS Peak P	71.92	63.90	ns	↓ 353.55 [90.00, 1063]	ns

Note. This table demonstrates the main effects of age group and piecemeal deglutition. Data for swallow parameters presented in Figure 7.4 are not shown in this table. Mann Whitney U Test was used for age group comparisons of *dominant swallow* data. Mean ranks presented, $p<0.05$ shows statistical significance. Kruskall Wallis Test for PD group main effect for *dominant swallow* data. Mean ranks (95% confidence interval lower and upper bounds) presented. All metrics represent pressure recordings in mmHg.

Figure 7.4. ***Swallow function variables affected by PD pattern and age group***



Note. Data are estimated marginal means based on the *dominant swallow* within the sequence. Mann Whitney U Test for overall age group effect. Kruskall Wallis Test for main Piecemeal Deglutition (PD) effects between PD pattern groups: Pattern A (1-2 swallows), Pattern B (3 swallows), Pattern C (4+ swallows), and pairwise comparisons (Bonferroni correction applied, p<0.016 shows significance). Swallow function variables were derived by Pressure Flow Analysis, AIMplot software via the *Swallow*

Gateway™ website. **A.** Velopharyngeal tongue base contractile integral. **B.** Upper Oesophageal Sphincter Maximum Admittance, the maximum admittance reading recorded within the UOS region during UOS opening. **C.** Upper Oesophageal Sphincter Integrated Relaxation Pressure, the median of minimum pressures recorded over 0.25 contiguous or non-contiguous seconds within the UOS region. **D.** Pharyngeal Distension-Contraction Latency, the average time from maximum admittance to peak pharyngeal contraction. **E.** Upper Oesophageal Sphincter Opening Time, the time from open to closure point set for the UOS. Graphs are presented with American spelling as produced by Swallow Gateway™.

7.4 Discussion

Our study aimed to determine whether PD impacts pressure flow metrics derived from P-HRM-I assessments. Additionally, we intended to characterise patterns of PD during P-HRM-I assessments in this paediatric cohort, asymptomatic of OPD. As ethical considerations protect healthy children from invasive testing, we evaluated recordings from a case series of children with uniform type IIIb oesophageal atresia (OA) who primarily underwent P-HRM-I investigation for oesophageal motility but were without symptoms of OPD. We observed a prevalent three swallow piecemeal sequence across the cohort. Furthermore, PD pattern types were associated with differences in swallowing biomechanics across the cohort and these changes were consistent with larger bolus volumes swallowed when fewer piecemeal swallows occurred. Age group specific differences in pressure flow metrics were evident between infants and children in this cohort; these variants were consistent with older children having a larger pharyngeal chamber. Additionally, we demonstrated a clinically relevant swallow selection method whereby the dominant swallow is identified in a PD sequence and, according to this cohort, provides sufficiently meaningful swallow function data.

The ability to discriminate between saliva and bolus swallows is paramount during manometric swallow assessments. As infants and young children seldom swallow on cue, swallow markers may not reflect the dominant swallow. Our results confirm our hypothesis that selection of the first swallow in a sequence may provide inaccurate indications of swallow function. Our findings suggest that assessors can reliably identify the dominant swallow, defined as the largest bolus

swallow based on the admittance curves and objective admittance values in a PD sequence; see Figure 7.1 A and B, thereby optimising the analysis process.

Whilst normative data are lacking in age matched paediatric cohorts, it is likely that larger than normal boluses will naturally elicit a PD sequence. In newborns and very young infants a volumetric dose-response has been reported in the pharynx whereby an increase in pharyngeal swallows occurred with increases in volumes (0.1, 0.3, 0.5 ml) (301). This work by Jadcherla and colleagues has also explored the newborn/infant pharyngeal swallow reflex and volume modulated responses in relation to respiratory patterns which indicate the intricate processes of airway protection during deglutition (219, 221). However, overall, paediatric piecemeal deglutition literature is limited; to our knowledge this is the first report of PD in the context of P-HRM-I assessments in children.

It has previously been shown that natural swallow volume during suckle feeding per swallow doubles to 0.4ml in the first month of life (302). However, a separate study by McGowan et al reported volumes of 0.26ml in a cohort of children during suck swallowing at 12 months of age (303). To our knowledge, single bolus volumes to indicate an upper limit tolerated (dysphagia limit) before multiple swallowing is required (304) has not been established in paediatric swallowing, however would help to differentiate physiologically normal PD from the multiple swallowing seen in the context of OPD. To date, PD has been described as a feature of OPD, whereby piecemeal or multiple swallowing indicates impaired lingual strength/movement, and pharyngeal swallow impairment (299, 300). Additionally, in the absence of obvious muscle weakness amongst patients, PD is clinically noted for possible swallow fear (phagophobia), hypersensitivity to large boluses, or retention of a suckle pattern due to developmental delay or disorders (299, 300).

It is important to note the volumes given in this study were offered according to the primary investigation of oesophageal motility which aimed to challenge the compliance of the oesophagus following OA repair. The P-HRM-I recordings have opportunistically been analysed as the pharyngeal segment was captured in this cohort of children asymptomatic of

OPD, who would not otherwise have undergone pharyngeal manometry assessment. Therefore, our study demonstrates that infants and children receiving a single oral bolus (2-5ml) during P-HRM-I assessment usually consume the bolus over three swallows (PD pattern B). We anticipated that children older than 12 months would show fewer PD swallows to clear the bolus from the oral cavity; however, the PD pattern distribution did not differ from that of infants, suggesting that PD is a fairly ubiquitous swallowing behaviour in both infants and children undergoing P-HRM-I assessment.

PD pattern A (1-2 swallows) was associated with differences in UOS relaxation pressure, pharyngeal flow timing and velopharyngeal contractility when compared to patterns B and C, that are consistent with previous reports that show a larger bolus volume impacts these swallow function variables (224, 244). Velopharyngeal contractility and UOS opening diameter were especially affected; both showing the greatest differences between PD pattern subtypes; see Figure 7.3 A & B. Importantly, without consideration for PD during P-HRM-I analysis, a low UOS admittance value could be misinterpreted as impaired UOS opening when in fact it is caused by the reduced bolus volume associated with PD.

We note that UOS integrated relaxation pressure was inconsistent between averaged and dominant swallow data; it was reduced for averaged PD data but increased for dominant swallow data. This finding is due to the fact that dominant swallows provide a larger bolus volume for analysis and, therefore, the UOS relaxation pressures are higher when compared to the averaged results. Nevertheless, we would advocate for selection of the dominant swallow analysis for interpretation of UOS IRP due to biomechanical plausibility and improved reliability of results from a larger bolus volume.

The paediatric age-related differences in some swallow function variables follow expectations for a relatively larger pharyngeal chamber amongst older children. For example, UOS relaxation pressures were *lower*, UOS opening diameter was *wider* (higher admittance) and distension-contraction latency was *longer* amongst older children compared to infants.

Additionally, hypopharyngeal intra-bolus pressure was *higher* which likely relates to a relatively larger bolus volume taken in older children i.e., 5ml compared to 2ml in younger patients.

We acknowledge the limitations of this study. Results are based on children with oesophageal atresia and, whilst it is established that oesophageal peristalsis is disrupted, the impact on oropharyngeal swallowing is less clear (305, 306). These children were considered suitable for this initial description of PD as pharyngeal swallow patterns were adventitiously captured during their investigations. A gold standard approach to exclude OPD (barium radiology or FEES) was not possible due to ethical constraints, however the attending doctor and parent reports confirmed each participant was asymptomatic of OPD. We propose that the data presented here are a close representation of unimpaired oropharyngeal swallowing in young children, in a population that ethically could not be assessed for pharyngeal function using the P-HRM-I methodology. Whilst saline may be unfamiliar to a child during the P-HRM-I assessment, saline swallowing is standard procedure for P-HRM-I investigations as it is highly conductive and optimises impedance recordings. Our retrospective analysis grouped the volumes given to participants (2-5mls) as the sample size (n=27) did not lend to statistical exploration of individual volumes. Bolus volume control in paediatric oropharyngeal swallowing is challenging due to anterior spillage and refusal, however, prospective studies with larger cohort sizes will need to address the lack of standard volume comparisons. Description of swallow patterns from a control group not undergoing P-HRM-I investigation may provide further details on the natural piecemeal patterns in this age group, however this was not ethically feasible or intended for this study.

7.5 Conclusion

Overall, this exploratory study demonstrates that PD patterns impact pressure flow metrics. We have highlighted key differences in the swallowing biomechanics between infants and children and in relation to PD pattern. All P-HRM-I swallow assessments should note and adjust for PD in order to accurately capture an individual's swallow function. We propose that the

dominant swallow within a piecemeal sequence provides a meaningful analysis of swallowing function and is simpler to perform than averaged PD data. The discrimination of the dominant swallow requires that impedance is recorded. We propose the dominant swallow data from a piecemeal sequence should always be interpreted in the context of the overall PD pattern observed. The causes for PD will depend on the clinical presentation and age for each patient. Therefore, to confirm these findings and build paediatric reference ranges, future studies should record PD patterns in children with oesophageal atresia with and without OPD, as well as other paediatric OPD cohorts.

Chapter 8: Pressure Flow Analysis for Assessment of Paediatric Oropharyngeal Dysphagia

The following chapter progresses the investigation of paediatric swallowing biomechanics with examination of children with clinical oropharyngeal dysphagia (OPD). Specifically, swallowing pathophysiology is described according to standardised clinical measures, in association with the most overt signs of OPD. Results are relative to a surrogate healthy control group, which is unique in the paediatric manometry literature.

I am first author of this chapter, now published[8]. I declare that I was principally responsible for writing the manuscript submitted for publication. I recruited all participants, acquired all high-resolution impedance manometry studies (P-HRM-I) and completed all data analysis. I was assisted by author Taher Omari with statistical analysis and interpretation of the findings. Please see the form in Appendix 8 with the statement of contribution from all co-authors of this chapter.

[8] Text in this chapter has been published as:

Ferris L, Rommel N, Doeltgen S, Scholten I, Kritas S, Abu-Assi R, et al. Pressure-flow analysis for the assessment of pediatric oropharyngeal dysphagia. J Pediatr. 2016; 177: 279-85. Reference (55).

8.1 Introduction

Safe, effective, and efficient swallowing throughout development relies on intricate sensory development, fine motor coordination of the swallowing musculature, and maturation of feeding skills to ensure airway protection and full bolus clearance from the oropharyngeal segment (184, 307, 308). Physiologically, pressure changes across the pharyngo-esophageal segment drive bolus movement during the swallowing process. Stimulation of mechanoreceptors in the base of tongue during bolus propulsion, and afferent pathways stimulated by bolus advancement into the oropharynx trigger the pharyngeal swallow response (309). The soft palate elevates to seal the nasal cavity; the cricopharyngeus (CP) muscle, which primarily generates the upper oesophageal sphincter (UOS) high pressure zone, relaxes in coordination with hyolaryngeal excursion to enable concomitant airway protection and UOS opening. The pharyngeal stripping wave follows to clear any bolus residue. In cases where there is restriction at the level of the UOS, bolus outflow from the pharynx is obstructed and intra-bolus pressures increase, making post-swallow residue and risk of mid or post-swallow aspiration more likely.

Children with developmental disorders, neurological conditions, respiratory or cardiac problems, oesophageal dysmotility or structural deficits such as cleft palate are at risk for oropharyngeal dysphagia (OPD) and potentially aspiration (12, 24-26, 34, 299, 310). The pathophysiology underlying OPD symptoms is important for diagnosis and management, however this is often difficult to determine in these children.

Objective assessment of oropharyngeal swallowing is challenging due to its mechanically complex nature (25). Pharyngeal high-resolution solid-state manometry with impedance (P-HRM-I) is a catheter-based diagnostic modality which overcomes some of the inherent limitations of existing assessment techniques. Used as an adjunct to videofluoroscopy swallow studies (VFSS), P-HRM-I enhances biomechanical evaluation of oropharyngeal swallowing and furthermore, pressure and impedance recordings generated during P-HRM-I-measured swallows can be analysed using Pressure-Flow Analysis (PFA) (153, 181, 184, 236, 239, 247). Published studies in adults and, to a lesser extent in children with pharyngeal dysphagia, have

shown individual PFA measures and a global composite score of OPD, the SRI, are able to discriminate consequences of swallowing pathophysiology, such as aspiration risk, the presence of post-swallow residue and abnormal pharyngeal distension-contraction timing in circumstances of poor oral containment and/or delayed swallow trigger (153, 181, 184, 206, 236). Whilst PFA measures differ in relation to the radiological picture of severity, it remains to be determined which PFA measures correlate with the degree of swallowing impairment determined by accepted clinical assessment scales that are widely used amongst speech-language pathologists.

The aim of this study was to perform P-HRM-I with PFA in a heterogeneous group of children with clinically recognised signs of OPD to investigate potential correlations with established clinical assessment scales, namely the Dysphagia Disorders Survey (DDS) (45), and the Functional Oral Intake Scale (FOIS) (311). We hypothesised that PFA metrics would differentiate OPD patients from non-OPD controls, and correlate with DDS and FOIS scores.

8.2 Methods

All investigations were performed in the Gastroenterology Department at the Women's and Children's Hospital in Adelaide, Australia. Children over 2 years of age with dysphagia symptoms were recruited between December 2011 and June 2015. The Women's and Children's Health Network Human Research Ethics Committee approved the study protocol (HREC1367). Informed consent was obtained from the primary care giver for all participants. Due to ethical concerns, healthy children were not studied; instead, children who were referred for manometric investigation of oesophageal motility were recruited as non-OPD controls. If needed, these children were given extra boluses with the catheter re-positioned to capture pharyngeal motor patterns.

8.2.1 Measurement Protocol

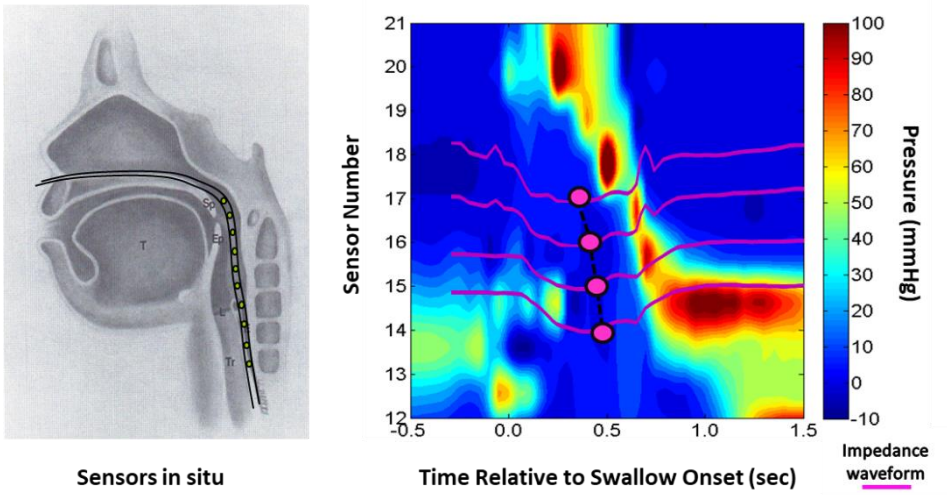
A 10 French solid-state HRM-I catheter was used, incorporating 25 1cm-spaced unidirectional pressure sensors, and 12 adjoining impedance segments, each of 2 cm (Unisensor AG catheter, Attikon Switzerland). The catheter was positioned trans-nasally with sensors straddling the entire pharyngo-oesophageal segment from velopharynx to proximal oesophagus. A small amount of water-based lubricant was used at the tip and shaft of the catheter to assist with passage. Once positioned, the catheter was taped to the participant's cheek. The pressure and impedance data were acquired at 20Hz (Solar Gastrointestinal acquisition unit Medical Measurement Systems, Enschede, The Netherlands). Patients were seated upright/semi-reclined for all swallows. The swallow material was offered via syringe or spoon and cervical auscultation was used to confirm swallow onset following bolus administration to the mouth. Liquid bolus swallows (saline 0.9% NaCl) of 2-5mls were recorded in each patient. Swallows acquired and analysed from P-HRM-I recordings were for liquid swallows without thickener modifications. [Note, the volume and number of boluses administered were determined on clinical grounds by the attending speech-language pathologist]. Patient recordings were included in this study if at least 3 swallows of 2ml saline were acquired. All non-OPD controls provided at least 4 x 5ml liquid (saline 0.9% NaCl) swallows. Saline was used to enhance conductivity for reliable impedance measurements. In order to investigate the effects of age and volume on the PFA measures in this cohort patients were grouped for age (2 to 5 years, 6 to 10 years, 11 to 14 years or 15-18 years) and volume (2 to 3ml or 4 to 5ml).

8.2.2 Acquired P-HRM-I Recordings

As shown in Figure 8.1, pressure recordings during swallows are displayed as colour isobaric-contour plots. This provides a graphical representation of pressure changes in real time, from the velopharynx to the proximal oesophagus during a swallow. Simultaneously acquired

impedance measurements detect the movement of the propelled bolus through the pharynx and UOS.

Figure 8.1. ***Sensor in situ and pressure topography***



Note. Schematic of catheter in situ with illustration of pressure sensors detecting isobaric contour pressure plot with embedded impedance waveforms (pink lines).

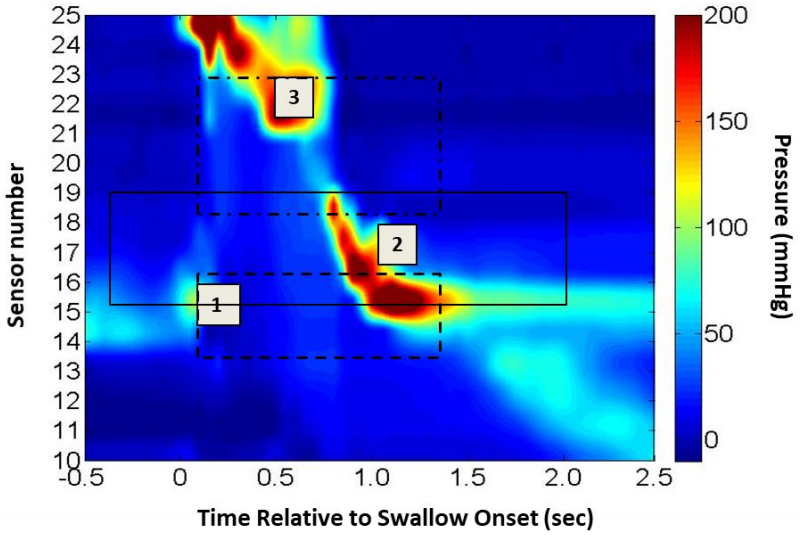
8.2.3 Pressure Flow Analysis

Following acquisition of the P-HRM-I recordings, pressure and impedance data for each swallow were exported as csv files and opened using purpose designed MATLAB-based software for PFA. (AIMplot.v1 software, copyright T Omari; version 7.9.0.529; MathWorks Inc., Natick, MA, USA). AIMPlot is used to derive swallow function metrics and an SRI. Derivation of metrics and the SRI have been previously described (181, 184, 236, 237). In brief, specific landmarks on the pressure topography space-time plot were selected to define specific regions of interest (ROI) for analysis; see Figure 8.2. The landmarks selected were: i) swallow onset, ii) position of the UOS proximal margin post swallow and iii) position of the velopharynx during the swallow.

Within each ROI, swallow function metrics were derived using automated algorithms. These metrics are: *pharyngeal peak pressure* (PP), defined as the maximum contraction of the pharynx during the swallow; the *pharyngeal nadir impedance* reading (NI), defined as a marker

of the centre and diameter of the main body of the swallowed bolus; the *pressure at nadir impedance* (PNI), defined as the intra-bolus pressure during maximal pharyngeal distension; the *time interval from nadir impedance to peak pressure* (TNIPP), measuring the time from bolus distension of the pharynx to the maximum pharyngeal contraction during the stripping wave; and the *flow interval* (FI), defining pharyngeal bolus dwell time (153, 181, 236, 247). Additionally, we measured the *UOS nadir impedance* (UOSNI) as a marker of UOS opening diameter (181), and the *UOS Resistance* (UOSRES) defined by UOS intra-bolus pressures over the relaxation period (236). The post-swallow impedance ratio (PSIR) is an integrated ratio that relates post-swallow impedance to the impedance during pharyngeal bolus passage. PSIR has previously been shown to elevate with post swallow pharyngeal residue seen on VFSS (237).

Figure 8.2. ***AIMplot Regions of Interest***



Note. The isobaric contour pressure plot showing region of interest (ROI) 1 to calculate PP, PNI and TNIPP; ROI 2 to calculate FI; and ROI 3 to calculate UOSNI and UOSRES.

The SRI is a separate composite score derived from four key swallow metrics previously found to differ in relation to aspiration risk (236). The SRI validation studies used simultaneous VFSS and P-HRM-I with AIMplot analysis and showed a significantly higher SRI in patients with penetration-aspiration compared to patients without penetration or aspiration (153, 236). Therefore, the SRI aims to quantify the overall level of OPD potentially predisposing to aspiration risk. This study provides the first non-OPD paediatric reference range data for the SRI. Using estimated marginal means with 95% confidence intervals, the cut off for normality for these data is < 8.

The SRI is derived by the following formula:

$$SRI = \frac{FI \times PNI}{PP \times (TNIPP + 1)} \times 100$$

All swallow function metrics investigated in this chapter are summarised in Table 8.1.

Table 8.1. ***Pressure Flow Parameters Investigated in this Study***

METRIC	DESCRIPTION	INDICATION
PP (mmHg)	Peak pharyngeal pressure	Pharyngeal contractile vigour
PNI (ohms)	Pressure at time of nadir impedance	Residual pressure during max. contraction
TNIPP (sec)	Time from nadir imp. to peak pressure	Bolus propulsion ahead of the stripping wave
FI (sec)	Flow interval	Bolus dwell time in the pharynx
UOSNI (ohms)	Lowest UOS impedance	Marker of max. bolus flow through UOS
UOSRES (mmHg/s)	UOS IBP divided by relaxation period	UOS IBP during relaxation
SRI	Swallow Risk Index	Aggregate score of swallowing risk
PSIR	Post-swallow impedance ratio	Bolus residue score

Note. This table demonstrates the descriptions and physiological indication of the pressure flow parameters investigated in this chapter.

8.2.4 Clinical Measures of Oropharyngeal Dysphagia

A speech pathologist not involved in routine care of the participants independently reviewed the medical records, interviewed the primary care givers and performed the Dysphagia Disorders Survey (DDS) assessment to determine the DDS scores, Functional Oral Intake Scale (FOIS) score and aspiration status for each patient as described below.

8.2.4.1 Dysphagia Disorders Survey

The DDS was completed within one week of the P-HRM-I recording. The DDS is a standardised dysphagia assessment tool used internationally for children 2 years and above (45). This two-part test provides a raw score and equivalent Disability percentile rank based on binary scored items of feeding competency (for liquids, separate to chewable, separate to non-chewable food types). Note, the higher the DDS score, the greater the dysfunction. Specific items 13 (Oropharyngeal swallow) and 14 (Post-swallow) of the DDS were also used to dichotomously define presence/absence of clinical signs of OPD during liquid swallows (based on observations of 'promptness' of swallow response, gagging, multiple swallows for a single liquid bolus, presence of cough, and/or wet breath/voice sounds).

8.2.4.2 Functional Oral Intake Scale

Functional Oral Intake Scale (FOIS) is a standardised benchmarking method indicating tolerance of consistencies based on clinical recommendation/intervention (311). Level 1 = nil by mouth; 2= tube dependent with minimal attempts of food or liquid; 3 = tube supplements with consistent oral intake of food of liquid; 4 = total oral diet of a single consistency; 5 = total oral diet of multiple consistencies but requiring special preparation or compensations; 6 = total oral diet with multiple consistencies without special preparation, but with specific food limitations; 7 = full oral diet, no restrictions. The patient group was then dichotomously grouped 1-3 or 4-7 as patients with FOIS 1-3 were tube dependent. Note that a score of 1-3 indicates children with most severe oral intake restrictions. Separately, fluid restrictions (use of thickener) were also dichotomously assessed.

8.2.4.3 Aspiration Status

Aspiration status from non-concurrent VFSS was a secondary outcome measure. Patient data were included if the VFSS was performed within 12 weeks from P-HRM-I investigations. Aspiration status was a binary retrospective measure based on clinical VFSS reports. Most clinical reports included Penetration Aspiration Scale scores which were independently reviewed for aspiration status by a speech-language pathologist who did not participate in the acquisition of VFSS or generation of reports. Patients were deemed aspirators if the clinical report outlined at least one episode of aspiration with thin fluids for all but one participant. For this one participant, thin fluids were not assessed as mildly thickened fluids were silently aspirated; this participant was included as an aspirator.

8.2.5 Statistical Analysis

All AIMplot software derived swallow function measures were averaged for each of the participants and non-OPD controls. A statistics package (IBM Corp. Released 2013. IBM Statistical Package for the Social Sciences (SPSS) Statistics for Windows, v. 22.0 Armonk, NY: IBM Corp) was used to investigate the data. Measurements were predominantly non-parametric therefore log transformations were completed prior to comparisons. DDS scores, as the only continuous outcome measure, were normally distributed for this cohort. Correlations used Pearson or Spearman's Rho Ranks; Group comparisons were based on Univariate Analysis, see Table 8.2; and Binary Logistic Regression was used for odds ratios and predictive values. Manual Bonferroni adjustments were calculated for all correlations ($p<0.005$) and SPSS Holm-Sidak adjusted p-values are quoted for multiple comparisons. A p-value <0.05 was considered to indicate statistical significance.

8.3 Results

8.3.1 Patient Details

There were 45 OPD patients recruited for this study on the background of suspected or established aspiration risk (26 males: 19 females; mean patient age: 5 years, range 2 – 18 years). Of these participants, 15 had a neurological diagnosis [cerebral palsy (8); neurodegenerative disorders (3); acquired brain injury (1); metabolic disorders (2); CHARGE syndrome with tracheostomy (1)]. In addition, 15 patients presented with global developmental delays. There were 7 patients with other medical conditions predisposing to aspiration risk: cardiac conditions (3); and 4 with structural abnormalities [repaired tracheoesophageal fistula + oesophageal atresia (1); laryngeal cleft (1); aberrant subclavian artery (1); and cleft palate repair (1)]. Additionally, there were 8 children with no known cause for dysphagia symptoms. There were 34 non-OPD controls (13 male: 21 female; mean age 12 years; range 2-18 years). These participants were recruited following clinical referral for lower oesophageal investigation (e.g. gastro-oesophageal reflux or rumination, or suspicion of oesophageal motility disorder). These patients had no history of oropharyngeal dysphagia and/or aspiration and did not demonstrate overt signs or symptoms of OPD.

8.3.2 Relationship between Clinical Measures and PFA measures

The relationships amongst PFA measures, DDS score, DDS criteria for clinical signs of OPD, FOIS, patient age and bolus volume are presented in Table 8.2. A higher DDS, presence of OPD signs and lower FOIS correlated significantly with PFA measures of dysfunction. Smaller volumes were swallowed by patients of younger age and/or more severe dysphagia. Therefore, patient age and bolus volume were included as co-variates for all subsequent group comparisons based on clinical signs of OPD to ensure that significant PFA measures were not due to these effects alone.

Table 8.2. ***PFA Measures and Age, Volume and Clinical Measures***

Metrics	Age	Volume	DDS	DDS clinical signs	FOIS
PP	0.13	-0.08	-0.03	-0.06	-0.12
PNI	-0.37**	-0.54***	-0.31**	-0.38***	-0.52***
TNIPP	0.14	**0.28***	**0.22***	**0.26***	**0.38*****
FI	-0.29**	-0.46***	-0.23*	-0.39***	-0.44***
UOS NI	-0.30**	-0.52***	-0.35***	-0.42***	-0.55***
UOS Resist	-0.48***	-0.48***	-0.27*	-0.32**	-0.62***
SRI	-0.42**	-0.53***	-0.34***	-0.45***	-0.55***
PSIR	-0.1	-0.23*	-0.17	-0.33***	-0.32***

Note. Correlation of PFA measures with key study outcome measures: DDS raw score, DDS clinical signs, and FOIS. Data presented are R values for Spearman Rank or Pearson correlations (bold). Significance *** p<0.005 following Bonferroni adjustment for multiple correlations.

An overall comparison of controls and patients revealed four key differences in PFA measures; see Table 8.3. The SRI, a global measure of dysfunction, and the PSIR, marking post-swallow residue, were both significantly higher in patients vs. controls ($p<0.05$ and $p<0.01$ respectively). Of individual PFA metrics, the FI was significantly longer ($p<0.05$) and the UOSNI was significantly higher ($p<0.01$) in patients.

Amongst OPD patients, UOS measures differentiated the patients with clinical signs of OPD on the DDS from those without clinical signs of OPD. Specifically, patients with clinical signs for OPD had higher UOSRES and significantly higher UOSNI compared to controls ($p<0.01$). UOSNI identified patients who did not show signs of OPD ($p<0.05$). These findings are consistent with reduced relaxation and UOS opening and contribute to OPD symptoms (Table 8.3).

Eleven OPD patients exhibited a FOIS of 1-3. These patients had a significantly higher UOSRES, higher UOSNI, and shorter TNIPP compared to non-OPD controls ($p<0.05$ for each respectively). Of the 45 OPD patients, 28 were recommended for thickened fluids as a management strategy for aspiration prevention. The PFA measures were not altered in these patients compared to patients taking thin liquids. A correlation between individual thickener levels and PFA metrics was intended, however the group sizes were unbalanced in those patients whose thickener level was available. The majority of patients were receiving nectar-thick fluids, while only 2 patients were receiving honey-thick and only a single patient was receiving spoon-thick fluids. The data were insufficient to allow comparisons of differences amongst the different thickener levels. Therefore, observations of PFA metrics in context of individual thickener levels will be incorporated in future studies.

Table 8.3. ***Pressure Flow Parameters and Clinical Measures***

PFA MEASURE	Controls	OPD Patients	Clinical Signs of OPD & Management					
			Overt Signs OPD		*Aspiration Presence*		*Functional Oral Intake Status*	
			NO	YES	NO	YES	4-7	1-3
PP (mmHg)	123 [99, 148]	119 [99, 140]	150 [110, 190]	114 [93, 134]	137 [93, 182]	77 [29, 125]	115 [94, 136]	142 [103, 180]
PNI (mmHg)	7 [2, 11]	14 [10, 17]	10 [1, 20]	16 [11, 21]	12 [1, 23]	10 [-1, 21]	13 [8, 18]	20 [11, 29]
TNIPP (s)	0.40 [0.37, 0.45]	0.37 [0.33, 0.40]	0.40 [0.33, 0.49]	0.35 [0.30, 0.39]	0.41 [0.32,0.48]	0.37 [0.28, 0.46]	0.40 [0.34, 0.37]	0.30[0.22, 0.37] [b]
FI (s)	0.50 [0.38, 0.66]	0.70 [0.61, 0.85] [a]	0.70 [0.42, 0.95]	0.80 [0.65, 0.90]	0.70 [0.42, 0.99]	0.72 [0.40, 1.00]	0.70 [0.58, 0.86]	0.90 [0.65, 1.10]
UOSNI (Ω)	192 [166, 218]	252 [231,273] [aa]	213[165,261]	271 [246,296] [bbc]	240 [183, 297]	238[187, 289]	254 [227, 281]	270 [222, 318] [b]
UOSRES (mmHg/s)	17.7 [10.0, 25.2]	24.8 [18.5, 31.0]	18.5[3.5, 33.3]	33.0 [25.0, 40.7]	28.7 [11.3, 46.0]	31.6 [14.0, 49.0]	24.0 [17.0, 32.0]	46.7 [33.5, 60.0] [b]
SRI	3 [-2, 8]	10 [6, 14] [a]	4 [-6, 14]	13 [8, 18] [b]	8 [-3, 19]	7 [-4, 19]	10 [5, 15]	13 [4. 23]
PSIR	73 [31, 116]	159 [124,193] [aa]	134 [52, 216]	155 [112,197]	105 [15, 194]	121 [31, 211]	148[104,191] [b]	157 [79, 235]

Note. Comparisons in relation to PFA measures for controls vs. patients; and in relation to Clinical Signs of OPD and Management Outcomes indicated by the FOIS. Data are estimated marginal means [95% Confidence Interval] compared using univariate analysis with age and volume as co-variables (with Sidak pairwise adjustments for multiple comparisons). [a] Patient group significantly different to control group. [b, c] Pairwise significance vs. controls [(b)] or No overt signs OPD/No aspiration[(c)]. ([a, b, c] $p<0.05$, [aa,bb,cc] $p<0.01$). Overt Signs OPD for liquid swallows according to the DDS i.e. presence of cough, wet breath/voice quality, multiple swallows, and/or delayed swallow sounds on cervical auscultation. Aspiration Presence based on VFSS conducted at WCH within a 12-week window from P-HRM-I study. Oral Intake Status based on FOIS.

There were 14 patients (31%) with an SRI above the upper confidence interval boundary measured for controls (SRI >8). A raised pharyngeal intra-bolus pressure (PNI) was the only one of the four key PFA metrics used to derive the SRI to be significantly associated with clinical signs of OPD. Patients with an abnormal PNI were nine times more likely to have clinical signs of OPD (Table 8.4). Regarding UOS metrics, abnormal findings for UOSRES and UOSNI were also significantly associated with clinical signs of OPD (Odds Ratio 9.7, $p = 0.016$ and 7.6, $p = 0.023$, respectively).

Aspiration status was gathered from clinical VFSS reports (performed within 12 weeks of P-HRM-I study). Aspiration status could only be determined for 19 of 45 OPD patients, 10 of whom showed no aspiration. Six of these 10 patients were reported to present with penetration only. Nine of the total 19 patients were reported to have aspiration of thin fluids. No PFA measures differentiated patients reported to be aspirating from those who did not aspirate on previous VFSS. Furthermore, presence of DDS signs of OPD or FOIS did not significantly differentiate aspirating patients from non-aspirating patients (Fisher exact test $p=0.09$, and $p=1.00$, respectively).

Table 8.4. ***Signs of OPD and The Likelihood of having Abnormal PFA Metrics***

Measure	DDS OPD signs		F exact p-value	Odds Ratio [CI]	p-value
	NO	YES			
PP					
Normal	6	4	0.508	0.776 [0.169, 3.558]	0.744
Low (<98mmHg)	23	12			
PNI					
Normal	9	1	**0.009**	9.240 [0.99, 85.64]	**0.05**
High (>11mmHg)	15	20			
TNIPP					
Normal	7	3	0.160	1.958 [0.39, 9.68]	0.410
Short (<0.38s)	16	19			
FI					
Normal	7	3	0.124	2.297 [0.45, 11.77]	0.319
Long (>0.64s)	15	20			

Note. Stratification of patients with/without OPD signs and symptoms and the associated normal/abnormal findings for the four key PFA metrics, which contribute to the SRI. Odds Ratios are based on Binary Logistic Regression with age, volume and normal/abnormal PFA measures as co-variables.

8.4 Discussion

In this study, we correlated objective PFA measures of swallowing function with clinically recognised signs of OPD in a heterogeneous cohort of children recruited with suspected or established aspiration risk. The majority of children with clinical signs of OPD had diagnosed neuro-myogenic conditions, such as cerebral palsy, muscular dystrophy, or clinically reported global developmental delays.

Participants with and without clinical signs of OPD were assessed using PFA swallow metrics as a method to objectively quantify pharyngeal and UOS motility and bolus flow patterns. OPD patients had higher SRI and PSIR, which are global PFA parameters consistent with greater risk of OPD. The SRI was abnormal (>8) in 25% of the patient cohort. Of the four key metrics used to calculate the SRI, abnormal pharyngeal intra-bolus pressure (PNI) was the only measure significantly linked to the incidence of clinical symptoms of OPD. Elevated pharyngeal

intra-bolus pressure (as measured with PNI) is a marker of flow resistance when pharyngeal propulsion is adequate. Given that the majority of patients (66%) in this cohort presented with pharyngeal pressures suggestive of normal pharyngeal propulsion, the elevated PNIs were most likely a consequence of resistance at the level of the UOS. Results for PFA metrics specific to the UOS high pressure zone provide further evidence of UOS dysfunction. Patients with clinical signs of OPD and a poor functional oral intake score (FOIS score 1-3) showed residual UOS pressures and significantly higher UOS impedance recordings during bolus flow. These markers indicate restricted UOS opening (218, 249).

Resistance at the level of the UOS during swallowing is a clinically important finding as it increases the risk of mid or post-swallow aspiration and/or post-swallow residue in particular at the level of the pyriform sinuses. Consequently, assessment of UOS dysfunction is considered essential for therapeutic decision making (254, 312). Whilst we demonstrate objective evidence that UOS dysfunction is prevalent in this paediatric OPD cohort, there is conjecture regarding the prevalence of UOS dysfunction in paediatric dysphagia. The literature is limited and mostly focused on previous case studies of extreme pathologies such as cricopharyngeal achalasia or in relation to hypertrophy and/or hyperactivity of the CP muscle secondary to GORD (229, 254, 312, 313). Our data suggest that PFA metrics, specifically within the UOS high pressure zone, may provide greater confidence for assessing and directing treatments for impaired UOS opening.

Whilst PFA results from this study have demonstrated clear features of UOS dysfunction in this paediatric cohort we acknowledge some limitations: P-HRM-I recordings were performed without simultaneous VFSS which could provide an indication of lingual propulsion, hyolaryngeal excursion and reliable aspiration status. The aspiration status used in this study was included retrospectively as a secondary measure of clinical interest. Aspiration status may have varied between VFSS and P-HRM-I studies (up to 12 weeks apart). Whilst there were some weak correlations between PFA metrics and DDS scores/FOIS scores, we note that presence of DDS signs of OPD or FOIS did not significantly differentiate aspirating patients

from non-aspirating patients. In the context of these limitations we also acknowledge the SRI did not differentiate aspirators and non-aspirating patients in this study. However, the main intention for this study was to focus on established clinical assessments, not radiological measures. We also note that a previous paediatric study with simultaneous VFSS and P-HRM-I was able to show significantly different SRI results between aspirating and non-aspirating patients (184). Another limitation is that the non-OPD control group were not age matched to the OPD patient group. Obtaining true paediatric control group is not possible for ethical reasons; therefore, children referred for clinical investigation of lower oesophagus were included as pharyngeal controls and age matching was not possible. While volume effects have previously been demonstrated, showing increased pharyngeal peak pressure with increased bolus volume (247), in this study bolus volumes could not be standardised due to differences in age, size and OPD severity. To address this limitation, volume and patient age were included as covariates for statistical analysis. We intend to stratify the aetiology for OPD in future cohorts and investigate the types of clinical signs of OPD; however, such statistical analysis was not reliable within this small sample size.

8.5 Conclusion

In conclusion, PFA analysis is a promising research tool that may in the future facilitate the clinical assessment of the intricate pharyngeal and UOS biomechanical characteristics of healthy and impaired swallowing. PFA analysis offers objective profiling of bolus timing and efficiency of bolus clearance with integrated recordings of pressure activity in the pharynx and UOS. In the cohort studied here, PFA findings suggest a higher prevalence of UOS dysfunction in paediatric OPD patients, which, based on these findings, suggests that patients could benefit from UOS-specific therapies and interventions. Further investigation is required.

Chapter 9:

Part 1: Repeat P-HRM-I studies in Children and the Factors that Influence Data Quality

Part 2: The Effects of Visit, Bolus Viscosity, Medical Condition, and Age Group on Pressure Flow Parameters

The preceding chapters in Section 2 described swallowing physiology in healthy volunteers studied to establish normative swallowing responses, and so far in Section 3 swallowing patterns and pathophysiology associated with dysphagia in children, have been described. In Chapter 8, altered swallowing biomechanics were demonstrated in children with OPD of broad aetiology, highlighting the value of P-HRM-I when diagnosing PFDs in children. It is particularly important to be able to track swallowing function over time in relation to growth and development, progression of a disease, and/or to determine outcomes from therapeutic interventions, therefore P-HRM-I assessments in children need to be repeatable. This chapter completes Section 3 and has two parts. Chapter 9, Part 1 investigates repeat P-HRM-I testing in children with a descriptive exploration of the factors influencing acquisition of analysable, high-quality data. Chapter 9, Part 2 examines swallowing pathophysiology according to the effects of visit, bolus viscosity, medical condition and age group.

9.1 Introduction

During a child's overall growth and development, dynamic anatomical and physiological changes occur, altering the characteristics of swallowing physiology. This is accompanied by the rapidly developing acquisition of feeding skills, which evolve as the child transitions from an exclusively liquid diet to more textured foods (6, 314). These developmental processes are critical for safe swallowing function and adequate nutritional intake, which in turn enable further physiological development of other domains in the growing child. However, the development of safe swallowing function can be interrupted by various conditions that predispose a child to OPD, including, but not limited to, neurological disorders, global developmental delay, structural abnormalities of the swallowing mechanism and prematurity of birth (3, 5, 9, 22, 26). Therefore, to be able to document longitudinal change as a function of growth and development, disease progression and/or outcomes of therapeutic interventions, diagnostic assessments need to be repeatable. There are currently no published paediatric repeated measures of P-HRM-I data that determine biomechanical changes in swallowing over a 12-month period. Given the complexity of these children's biopsychosocial needs, as well as the relative novelty of P-HRM-I as an assessment of swallowing in this population, one aim of the study described in this chapter was to investigate the key influencers for successful completion of P-HRM-I studies as defined by acquisition of analysable data and patient return rates. This was considered noteworthy, as sharing this experience may inform and improve planning and outcomes of future paediatric P-HRM-I research and/or clinical studies. Therefore, we evaluated and report on factors and practices that were perceived to have contributed to successful P-HRM-I study completion. In addition, P-HRM-I data collected from a pilot sample of reliably repeated studies were examined to determine the effects of background medical condition, age group and bolus viscosity on a range of pressure flow parameters.

It is acknowledged that other instrumental assessment tools, including VFSS and FEES can be repeated in the paediatric population. However, deriving objective, quantitative paediatric measurements has not been achieved with FEES, and with the application of VFSS, the

paediatric literature is currently limited (90, 100, 101). Furthermore, repeat VFSS testing is not conducted within a 6-month window as radiation exposure dose limits are especially restrictive in paediatric patients, who are at a greater risk, in comparison to adult patients, of malignancy due to radiation exposure (75, 102, 315). Similarly, the implementation of FEES is centre-specific, dependent on staff expertise, and is especially limited regarding quantification of swallowing biomechanics (105). While the evidence of P-HRM-I is also limited in children, its potential for quantitative measurement of paediatric swallowing pathophysiology is promising (19, 54, 184) and unlike VFSS, can be repeated without risk of excessive radiation exposure.

Therefore, the purpose of this study was two-fold: i) to explore the influencing factors of repeat testing, return rate and generation of analysable data in a paediatric cohort (with description of our clinical procedure as it developed over the 4-year period of data acquisition) and ii) to investigate the effects of visit, bolus viscosity, medical condition and age group, in a pilot set of repeat paediatric data recorded over two visits.

9.2 Methods

The data acquired in this study are presented in two parts. The first part outlines participant group details, factors influencing repeat testing and endpoint analysable data, and lessons learned from our paediatric P-HRM-I clinic. The second part presents quantitative pressure flow parameters results only for those children who participated in both visits, from whom analysable data were collected. The effects of visit over two timepoints, bolus viscosity, medical condition, and age group are investigated. A cut off of 4 years of age was used to stratify our cohort for statistical analysis of age group (i.e. above and below 4 years of age), as has previously been reported, based on the anatomical differences of the swallowing mechanism unique to children below 4 years of age (51).

9.2.1 Ethics

The Human Research Ethics Committee at the Women's and Children's Hospital approved this prospective study (HREC 1367/04/2020) and children were enrolled with parent/guardian consent between the ages of 6 months to 18 years if they demonstrated symptoms of OPD and were receiving oral intake with or without alternative feeding methods. Patients ≥15 years of age independently provided written consent to participate. Any child nil by mouth was excluded from the study. Enrolled participants presented for two visits, 12 months apart. Following each visit, a manometry report was generated and shared with clinicians involved in caring for each child's swallowing needs. However, families were informed prior to participation that manometry results would not primarily direct clinical care and management.

9.2.2 High Resolution Pharyngeal Manometry Procedure

All manometry procedures were carried out through the Gastroenterology Department at the Women's and Children's Hospital, Adelaide, in the presence of a research nurse, SP, and manometry technician. Patients were fasted for a minimum of 3 hours prior to P-HRM-I procedure, and a 10 French solid-state unidirectional high-resolution manometry catheter (32 pressure sensors spaced at 1cm, and 16 impedance segments spaced at 2cm segments, Unisensor/Laborie, Attikon, Switzerland) was used to collect data. Catheter sensors detected pressures along the swallowing mechanism from velopharynx to proximal oesophagus. Adjacent impedance electrode segments simultaneously detected bolus contact. On completion of each study, the de-identified P-HRM-I data file was exported as an ASCII file and uploaded to the Swallow Gateway™ portal for algorithm analysis of swallowing pressure and admittance waveforms. Definitions for all pressure flow parameters can be reviewed in Chapter 4, Table 4.1.

9.2.3 The P-HRM-I Acquisition Protocol

Once the P-HRM-I assembly was positioned, the catheter was taped to the child's face, tucked over their shoulder, and loosely taped to their clothing to reduce movement and avoid temptation for the child to tamper with the catheter. Following at least a 5-minute accommodation period, saline boluses (0.9% NaCL) between 2-5ml were offered, dependent on a child's age and clinical capability. Additionally, a viscous bolus medium (EFT Viscous, Sandhill Scientific, Highlands Ranch, CO, USA) was used as recommended by a Manometric Medical Measurement Systems consultant at the time of data collection (2012-2016). Since this time, further testing of bolus conductivity and viscosity was undertaken by our research group and revealed inconsistencies and limitations in the EFT Viscous product. These details are relevant to the context of the second component of the study as it unfortunately rendered three impedance-based swallowing metrics unreliable. These are hypopharyngeal IBP, UOS maximum admittance (max Ad), and the SRI. Therefore, only pressure or timing related measures are reported in the second part of this study.[9] All swallows were analysed via Swallow Gateway™, and piecemeal deglutition was formally assessed with the largest bolus swallow selected for analysis from a piecemeal sequence.

9.2.4 Acquisition of Participant Group Details

Data for the participant group details, their enrolment, and factors that influenced return rate were all acquired via correspondence notes made within a study notebook and Excel spreadsheet kept throughout the recruitment phase of this study. Additionally, within each participant case report form (CRF), notes were kept in relation to study tolerance and bolus trials taken i.e., volumes and bolus types. All documentation was reviewed to determine the results shown in Figure 9.1. Studies were assessed and considered adequate/analysable according to the following standard: a minimum of two swallows was acquired, of at least 2ml

[9] To overcome this shortfall, a standardized swallow bolus medium (SBM) kit was developed (in 2017) in collaboration with food company Trisco©. See Chapter 4, Section 4.2.

bolus volumes of liquid saline and/or EFT Viscous. A summary of the procedural approach used during P-HRM-I data acquisition and relevant lessons learned is included below. These procedures were evolving, as is the nature of this element of action research, therefore are included in the Results section.

9.2.5 Statistical Analysis

Statistical analysis using SPSS (IBM Corp. IBM Statistical Package for the Social Sciences [SPSS] Statistics for Windows, v. 25.0 Armonk, NY: IBM Corp) was applied to the average P-HRM-I results for each bolus condition (saline or viscous) for each participant and visit. Data with a skewed distribution were normalised by log or square root transformation prior to analysis. Exploratory Generalised Linear Mixed Model analysis was used to evaluate the main effects of visit, viscosity, medical condition, and age group. Bonferroni adjustments were applied for pairwise comparisons. Main effect results are presented in Table 9.1.

9.3 Results

9.3.1.1 Our Approach to Conducting P-HRM-I Studies in Paediatric Patients

To optimise patient and family engagement for what is considered a relatively invasive investigation, a streamlined approach was needed. Following study enrolment based on informed consent, caregivers were contacted by phone the day before the P-HRM-I study and given (or reminded, if returning for a repeat study) clear instruction on how to find the clinic room. This contact also aimed to build rapport with caregivers and reduce any additional stressors in the lead up to the P-HRM-I study. It allowed discussion surrounding any concerns parents may have about the procedure, and the SP was able to ensure the participant was not suffering respiratory illness that may inflame the nasal cavity or pharynx and contraindicate the investigation. During this phone call, study details were outlined/reiterated clearly by the SP to familiarise and build a sense of predictability of the requirements of the appointment, e.g., the

need for the participant to fast for 3 hours prior, for caregivers to complete further paperwork when they arrived with the assistance of the SP/nurse. The procedure for catheter placement was also explained/reiterated.

Upon arrival at the Gastroenterology department, children were encouraged to remain with caregivers in the waiting room, where toys/activities were available. While all paperwork was completed, the research team finalised catheter calibration and study preparations, including weight and height measurements were completed prior to the child entering the clinic room. As children were required to fast prior to the appointment, caregivers were encouraged to keep all food/drink out of sight until the end of the study.

The clinic room ambience was adjusted by dimmed lighting, and instead of offering a range of distractions, caregivers were encouraged to choose one activity/toy to engage the participant with during the procedure. If the TV was in use, the volume was lowered to avoid loud and alarming noises.

Once the child was ready to enter the clinic room, an effort was made by all team members present to remain calm and avoid unnecessary and loud conversations. The child was welcomed into the clinic room with an age-appropriate toy or activity offered by one team member. This approach evolved from learning that children became easily overstimulated by excessive distractions and input from multiple team members. During catheter placement, some children (between the ages of 1 to 4 years) were wrapped in a sheet to restrict their body movements and avoided the caregiver from having to restrain their child during this process. Caregivers were encouraged to remain with their child throughout the study, however, were offered the option of leaving the room during catheter placement if they preferred. Once the catheter was taped and secured, a 5-minute accommodation period allowed the child to settle.

During this research program, a research nurse was responsible for all catheter placements. Midway through the 4-year acquisition period (in early 2015), the research nurse underwent hypnotherapy certification, which informed her practice in the following ways:

- carefully chosen and age-appropriate wording was used, avoiding words with pain connotations. Phrases such as ‘I’m going to touch your nose soon, you may feel something, you may not’, ‘it might tickle it might not’ were used.
- relaxation strategies were chosen together with the caregiver, such as hand holding/stroking from caregiver/foot massage from caregiver or another technician.
- in children with adequate receptive language skills, more specific imagery-based techniques were used to engage the child in their imagination. An example of this was a 5-year-old boy with Trisomy 21, who engaged in play with the research nurse and a batman figurine toy. He was led by the nurse to imagine the hospital sheet was his Batman cape, which was loosely wrapped around him during successful catheter placement. The conversation continued to focus on Batman while bolus trials were taken.

When each study was complete, the research nurse removed the tape and catheter, and the child was offered familiar refreshments brought from home. The family remained in the clinic room or waiting room for 15 to 30 minutes observation post extubation before leaving. The following section explores the details of the study group to determine the influencers of P-HRM-I analysable data.

9.3.1.2 Factors Influencing Acquisition of Analysable P-HRM-I Data

The influences on analysable data relate to the ability for a child to provide at least 2 swallows of at least 2ml saline and/or EFT Viscous. Therefore, bolus volume taken, and bolus conductivity were two key factors which affected analysable data acquisition. In total, 105 children were enrolled and underwent an initial P-HRM-I study, of which 71 produced analysable data. As shown in Figure 9.1, 17 of 105 participants were excluded from visit 1 due to an inability to provide at least 2 swallows of 2ml volumes, liquid or viscous. A further 9 of 105 children were excluded from visit 1 studies due to compromised bolus conductivity. These children refused saline or EFT Viscous, instead opting only for food/drink brought from home,

e.g. chocolate milk/juice. As this study was conducted for research purposes only, children were offered both consistencies (saline and EFT Viscous) with minimal coercion, and while improvement of bolus conductivity of these home foods was attempted (i.e. saline added to milk/juice products), these studies have been excluded from the final dataset to uphold standardisation of the bolus conditions for comparison within and between participants, across visits. Eight of 105 children poorly tolerated the study at visit 1 (4 males, 4 females; mean age 11 months old; 2 children with neurological conditions; 1 child with GDD, and the remainder characterised by aspiration risk with no known underlying medical diagnosis). Therefore, these studies were ended before bolus swallows were captured.

Of the 71 children who produced analysable data in their first P-HRM-I assessment, 39 (55%) returned for a second visit 12 months later. Of these 39 children, 24 produced analysable data. Four of 39 were excluded as fewer than 2 swallows of 2ml volumes, liquid or viscous were acquired. Averages of at least 3 swallows were achieved for 94 % of the participating cohort, and saline and viscous boluses were taken during both visits in 80 % of the cohort. A further 5 of 39 children were excluded as their swallows comprised poorly conductive food/liquids. The repeat study was poorly tolerated in 4 of 39 participants (2 males, 2 females; mean age 3.5 years, each with a different medical condition: 2 children with GDD, 1 child with a neurological condition, 1 child with a cardiac condition). A further 2 studies presented unexpected technical incompatibility and were subsequently excluded despite good tolerance and reliable bolus swallowing. Overall, of the total 144 HRM studies performed across two visits in our study, 49 of 144 (34%) were excluded due to unusable data or poor tolerance (note this includes studies which were excluded due to technical issues; these were rare and do not reflect patient tolerance). The distribution of all 144 studies, by age groups is shown in Figure 9.2, stratified as follows: 0-4 years, 5-10 years, and 11-18 years of age. This demonstrates that tolerance and analysable data are most difficult to acquire in the youngest patient group, 0-4 years of age.

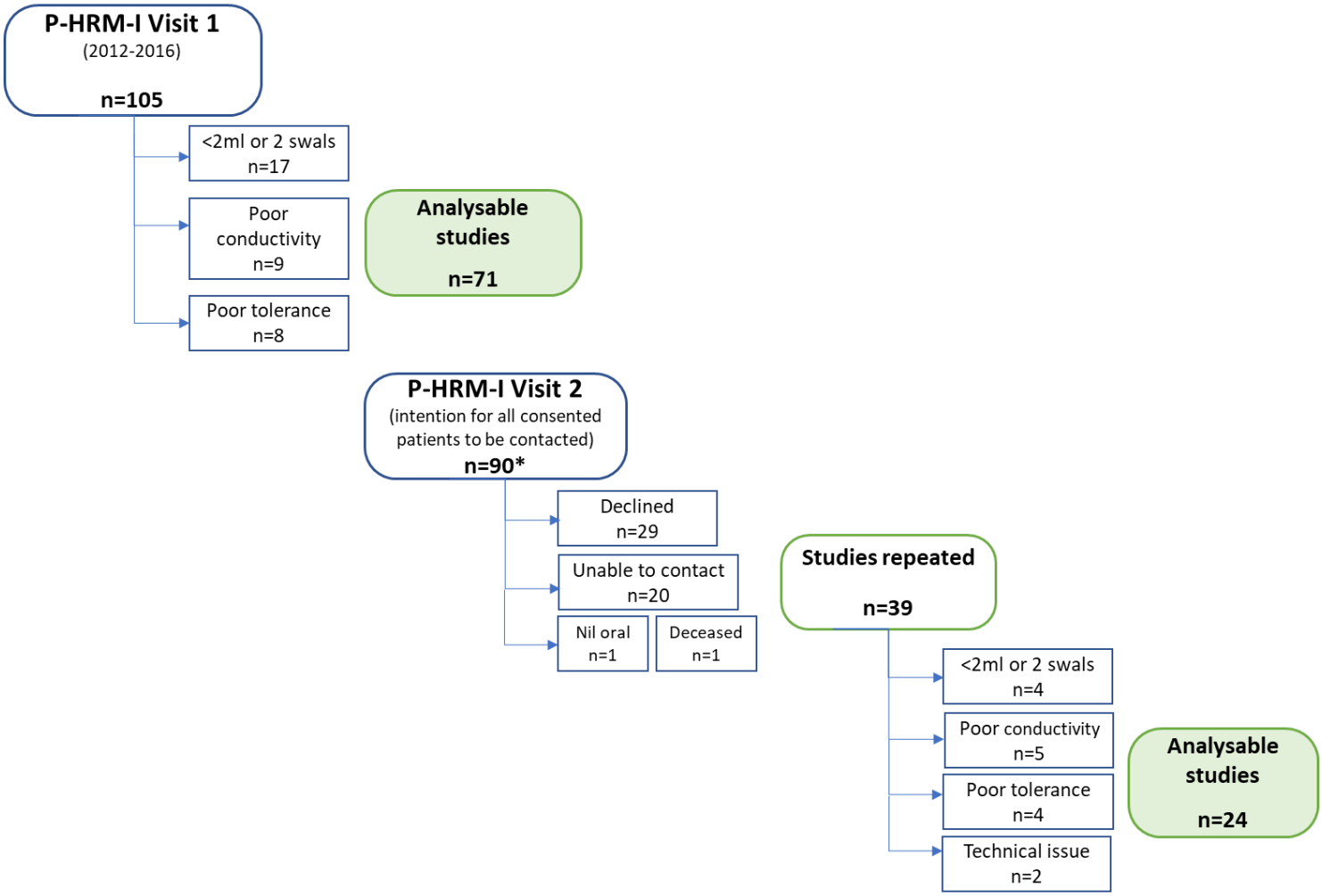
The following section stratifies the cohort and explores the details of the study group to determine the influencers of P-HRM-I repeatability and return rate for visit 2. Additionally, factors which affected the resulting analysable data at both investigation time points (visit 1 and visit 2) are outlined.

9.3.1.3 Factors Influencing Repeat P-HRM-I Studies in this Paediatric Cohort

The full cohort studied at visit 1 (105 families) was intended to be offered a repeat P-HRM-I investigation regardless of the outcome of their visit 1 P-HRM-I study. Unusable data at visit 1 did not restrict participation for visit 2. Ninety[10] of 105 families were invited to repeat the P-HRM-I investigation 12 months following enrolment. See Figure 9.1 for details of inclusion and exclusion in the final repeat dataset. Twenty-nine of these 90 families (32%), 4 of whom had moved from South Australia, declined a repeat study, with the primary reason given as avoiding an extra hospital visit, when the study was not clinically indicated. A further 20 families (22%) did not respond to phone call or letter invitation. One patient with a rare and complex metabolic condition had been made nil orally since visit 1, and one patient with a complex medical history on the background of severe quadriplegic cerebral palsy (CP) was deceased. Therefore, total repeat studies were conducted in 39 patients.

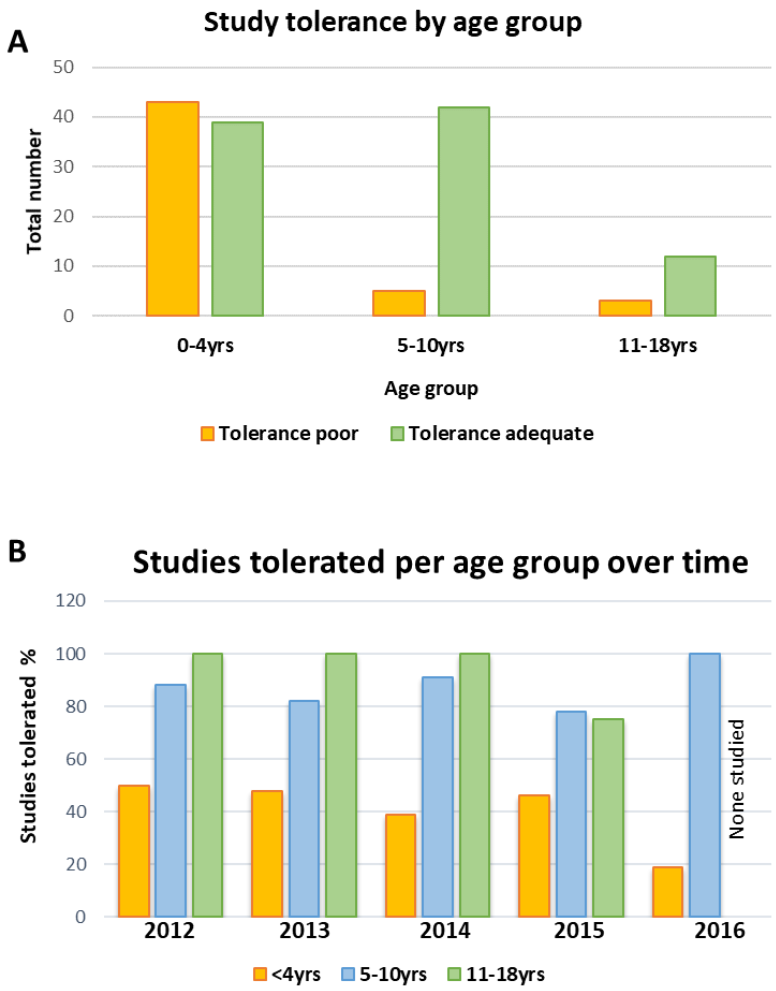
[10] The candidate's early maternity leave led to the inability to contact the final 15 families for a repeat study.

Figure 9.1. ***Flow Chart of Paediatric Studies between 2012 and 2016***



Note. This flow chart demonstrates the factors which influenced repeatability and acquisition of analysable data in a single paediatric cohort recruited between 2012 and 2016. *Contact of the remaining 25 patients was ceased due to early maternity leave.

Figure 9.2. ***Study Tolerance by Age Group***

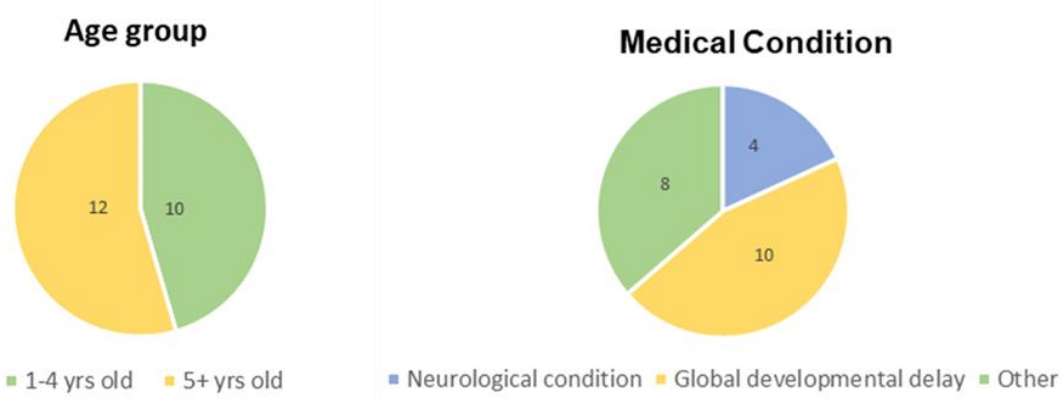


Note. This figure demonstrates the stratification of the study cohort into three age groups to illustrate distribution of study tolerance. Panel A illustrates tolerance of total studies per age group. Panel B illustrates percentage of studies tolerated per age group over time.

9.3.2 Quantitative Data from Repeat P-HRM-I Measurements

In this component of the study, a standardised protocol was followed for the entire cohort but only data on 22 children who underwent repeat P-HRM-I investigation are presented. A further 2 patients who did not remain neurologically stable across the 12-month period were excluded from the final statistical analysis, which brought the repeat test subgroup from 24 to 22. These two patients were excluded from the final statistical analysis as the remaining cohort were otherwise neurologically stable across the 12-month period. The exclusions were as follows: one child with a motor vehicle accident acquired brain injury attended for both visits but made significant gains in neurological function from initial to repeat manometry investigation; another child with a neurologically degenerative condition attended for both visits, tolerated the procedure very well however was excluded from the final analysis. The final dataset of 22 children (9 females, 13 males, mean age at visit 1 = 5.2 years) supplied adequate, analysable data for quantitative analysis of swallowing biomechanics. Effects of study visit over two timepoints, bolus viscosity, underlying medical condition and age group were investigated. The subgroup included in this analysis stratified by age group and medical condition is displayed in Figure 9.3.

Figure 9.3 ***Repeat Study Cohort Distribution by Age Group and Medical Condition***



Note. This figure shows the distribution of n=22 for age group and medical condition.

9.3.3 Pressure Flow Parameters Generated via Swallow Gateway™

A summary of the effects of visit, viscosity, medical condition and age group are included here. The significant effect of medical condition on pharyngeal contractility metrics is presented in Figure 9.4. A summary of all exploratory statistical analyses is shown in Table 9.1.

9.3.3.1 Effect of Study Visit

When comparing P-HRM-I outcomes between visits 1 and 2, there was no overall significant differences to any pressure flow parameters. As growth and development is most rapid in children <4 years of age, we investigated this subgroup (mean age at visit 1, 1.8 years) separately; however, all comparisons between study visits remained non-significant. Data were examined in relation to FOIS status, DDS and Dysphagia Management Staging Scale (DMSS: an adjunct to the DDS which provides a severity level of symptoms) and overall differences for the group remained unchanged (Pearson Chi-Square p=0.66, and p=0.83 respectively).

9.3.3.2 Effect of Viscosity

An increase in bolus viscosity led to a reduction in UOS basal pressure (UOS BP) ($F=4.07$, $p=0.05$), shorter distension contraction latency (DCL) ($F=10.02$, $p=0.002$), and elevated UOS integrated relaxation pressure (UOS IRP) ($F=6.94$, $p=0.01$).

9.3.3.3 Effect of Underlying Medical Condition

A key finding specific to the effects of medical condition was a significant difference in all pharyngeal contractility metrics: pharyngeal contractility integral (CI) ($F=11.93$, $p<0.001$); velopharyngeal CI ($F=11.00$, $p<0.001$); mesopharyngeal CI ($F=8.30$, $p<0.001$); and hypopharyngeal CI ($F=6.58$, $p=0.002$) were all significantly impacted by medical condition, in that patients with neurological diagnoses, all with spastic quadriplegic CP, generated higher pressure values compared to all other participants. One child with CP presented with

Gross Motor Function Classification System (GMFCS) level IV[11], and the remaining three children with CP presented with level GMFCS V[12]. Pairwise comparisons are shown in Figure 9.4.

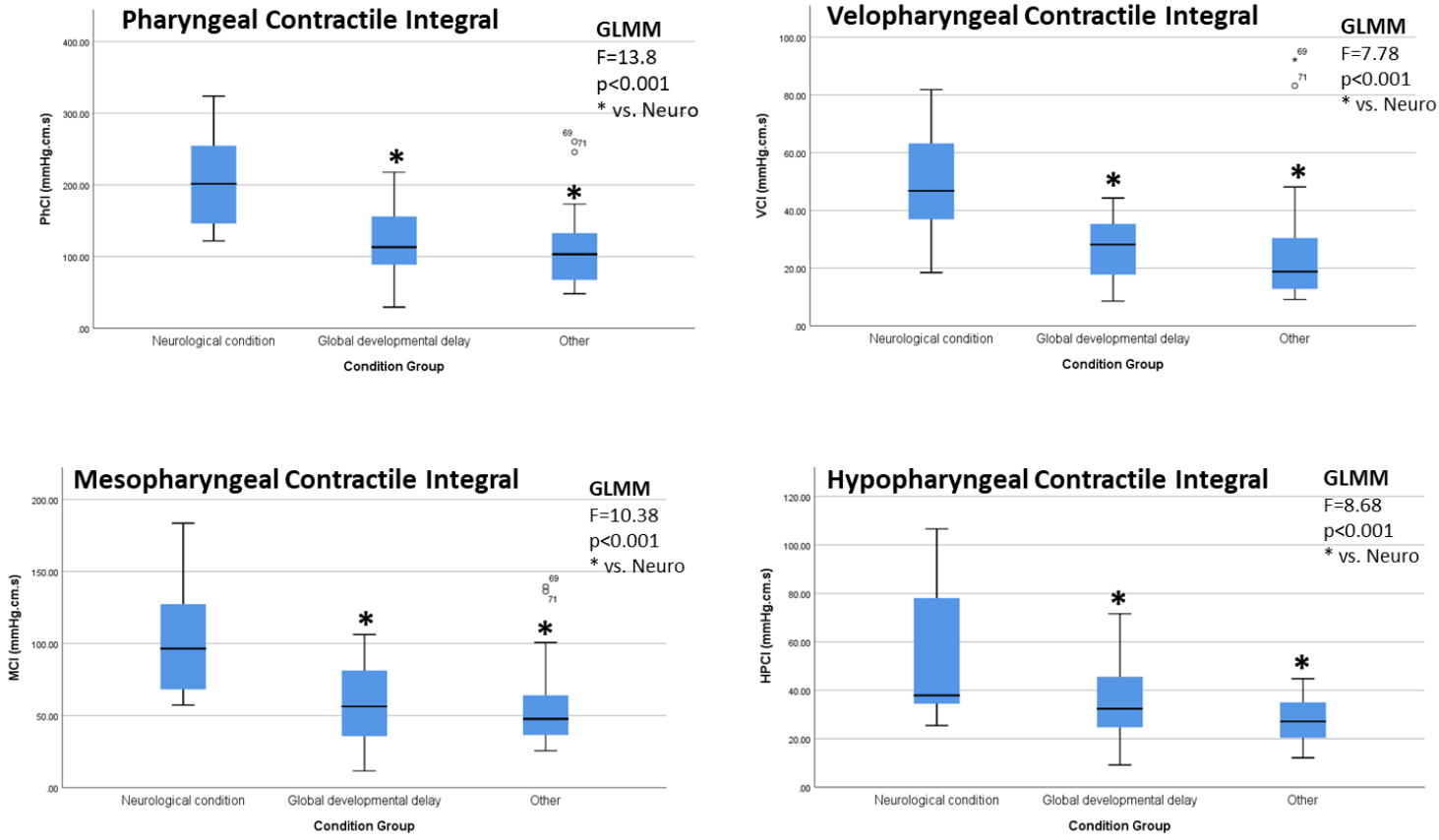
9.3.3.4 Effect of Age Group

Children >4 years of age had greater velopharyngeal CI (F=6.56, p=0.01), UOS CI (F=6.22, p=0.02) and proximal oesophageal contractile integral (PCI) (F=8.71, p=0.004) compared to children <4 years of age.

[11]Children may maintain levels of function achieved before age 6 or rely more on wheeled mobility at home, school, and in the community. Children may achieve self-mobility using a power wheelchair.

[12]Physical impairments restrict voluntary control of movement and the ability to maintain antigravity head and trunk postures. All areas of motor function are limited. Functional limitations in sitting and standing are not fully compensated for through the use of adaptive equipment and assistive technology. At Level V, children have no means of independent mobility and are transported. Some children achieve self-mobility using a power wheelchair with extensive adaptations.

Figure 9.4. ***Pharyngeal Contractile Integrals and Underlying Medical Condition***



Note. This figure demonstrates pharyngeal contractile integrals according to participant medical condition, demonstrating that children with a neurological condition (all with spastic quadriplegic CP) generated significantly elevated pharyngeal contractility at all regions, compared to children with GDD and other medical conditions.

Table 9.1. ***The Effects of Visit, Bolus Viscosity, Medical Condition and Age Group***

CORE OUTCOME SET METRICS						
Variable Subtype	**Variable**	**GLMM parameters**	**Repeat Visit Effect**	**Bolus Viscosity Effect**	**Medical Condition Effect**	**Age group Effect**
Pharyngeal lumen occlusive pressure	Pharyngeal contractile integral (PhCI)	*F* *P*	0.65 ns	0.17 ns	↑ **11.93** **<0.001**	↑ 3.44 0.07
	Velopharyngeal contractile integral (VCI)	*F* *P*	0.01 ns	0.47 ns	↑ **11.00** **<0.001**	↑ **6.56** **0.01**
	Mesopharyngeal contractile integral (MCI)	*F* *P*	1.11 ns	0.42 ns	↑ **8.30** **0.001**	1.72 ns
	Hypopharyngeal contractile integral (HPCI) *	*F* *P*	0.67 ns	0.33 ns	↑ **6.58** **0.002**	1.59 ns
Hypopharyngeal intrabolus distension pressure (IBP)						
UOS relaxation & opening	UOS integrated relaxation pressure (UOS IRP)	*F* *P*	0.53 ns	↑ **6.94** **0.01**	2.11 ns	↓ **20.9** **<0.001**
	UOS relaxation time (UOS RT)	*F* *P*	0.83 ns	0.11 ns	0.01 ns	↑ **15.36** **<0.001**
	UOS maximum admittance (UOS Max Ad)					

ADDITIONAL TO CORE OUTCOME SET SWALLOW GATEWAY™ SPECIFIC METRICS						
Variable Subtype	**Variable**	**GLMM parameters**	**Visit Effect**	**Viscosity Effect**	**Medical Condition Effect**	**Age Effect**
UOS contractility	UOS contractile integral (UOSCI) *	*F* *P*	0.001 ns	0.00 ns	1.00 ns	↑**6.22** **0.02**
	UOS basal pressure (UOS BP)	*F* *P*	2.60 ns	↓**4.07** **0.05**	0.27 ns	0.39 ns
	UOS peak pressure (UOS PP) *	*F* *P*	↓3.12 0.08	0.09 ns	0.02 ns	0.32 ns
Proximal oesophageal contractility	Proximal oesophageal contractile integral (PCI) *	*F* *P*	1.10 ns	0.06 ns	0.07 ns	↑**8.71** **0.004**
Flow Timing measures	Pharyngeal distension-contraction latency (DCL)	*F* *P*	0.008 ns	↓**10.02** **0.002**	↓2.70 0.07	1.38 ns
	Bolus presence time (BPT)	*F* *P*	1.82 ns	1.49 ns	0.46 ns	0.002 ns
Global Swallow Risk Index						

Note. This table shows a subgroup of neurologically stable patients who attended for a successful initial and repeat study, n=22 (9 females, 13 males, MA at visit 1 = 5.2 years), with 2-5ml saline and/or EFT bolus product swallows acquired. Viscosity effects ↑ ↓ compared to saline. Binary age groups to investigate impact of patient size, ↑ ↓ compared to children 1-4yrs of age. Additionally, medical condition effects presented, ↑ ↓ compared to neurological diagnosis (CP). GDD, neurological diagnosis and 'other' causes of OPD, no patients with structural abnormality in the 5+years age group. * depicts metrics that were LG10 transformed for General Linear Mixed Models analysis. The pressure flow parameters in grey bars were excluded from analysis due to bolus conductivity limitations.

9.4 Discussion

To our knowledge, this is the first report of repeat P-HRM with impedance measurements within a single paediatric cohort. As outlined in the first part of this study, multiple factors appear to influence endpoint analysable data and repeat testing of the manometry technique in children. Manometry assessments are challenging in children, and the strategies outlined in Section 9.3.1.1 aimed to encourage calmness and composure in caregivers and participants throughout the procedure. The main intention of employing such strategies is to enhance success with bolus trials, but a twofold benefit may occur whereby overactivity of the UOS known to be a reflexogenic region, substantially altered by factors such as stress and anxiety (316), may also be reduced. In combination with the 5-minute accommodation period following catheter placement, these considerations intend to improve the reliability of P-HRM-I recordings in children. The final dataset outlined in the second part of this study shows swallowing biomechanics in relation to the effects seen by visit, bolus viscosity, medical condition and age group in a neurologically stable patient cohort. Changes relating to growth and development expected between visits, over the 12-month period, were not detected in this study.

9.4.1 Factors Influencing Analysable Data and the Lessons Learned from Conducting P-HRM-I Studies in Children

Conducting P-HRM-I procedures in children poses unique challenges related to several factors: discomfort with the nasogastric catheter placement (particularly among children between the ages of 12 months and 3 years of age); learned avoidance of medical investigations due to past negative or painful experiences, e.g. blood tests in some children; and compliance with procedure-specific requirements, e.g. volumes and conductivity of bolus types can be challenging to persuade a child to swallow. Of the total P-HRM-I procedures performed in this study, 34% were excluded due to unusable data or poor tolerance. This reflects the evident challenges that must be minimised to make P-HRM-I assessments worthwhile in children. Through a variety of experiences across the data acquisition phase, we observed that children tolerated the study and performed better with less distraction and less stimulation, as described in 9.3.1.1. While the implementation of calming techniques most likely improves the overall experience for families and staff members, the stratification of the cohort by age group clearly reveals that a child's age is the greatest predictor of analysable study data. Below 4 years of age, there is at most 50% chance that a study will be tolerated, as shown across 5 years of data acquisition in our centre. For this reason, clinicians should be clear on the expectations of performing P-HRM-I tests in children below 4 years of age.

Beyond catheter tolerance, generating analysable data in P-HRM-I studies first and foremost requires standardised conductivity of the bolus and adequate volumes for reliable analysis of admittance data. The importance of optimising the conductive properties of all P-HRM-I bolus trials is emphasised, as limitations in the original viscous bolus product (EFT Viscous) utilised in this study were observed in this research. Standardised bolus preparations, such as the SBMkit™, are required for reliable bolus flow recordings and accurate generation of impedance dependent metrics. This will also ensure comparable within- and between-patient measurements, particularly if repeat studies are anticipated for a child, e.g. pre- and post-therapeutic intervention, such as botox therapy in UOS achalasia.

Another key factor for consideration during acquisition of paediatric P-HRM-I data is the documentation of bolus volumes swallowed, and the number of swallows captured per bolus condition i.e. volumes and viscosity levels. While this study required a minimum of 2 swallows for inclusion, we recognise that in the case that a single swallow is captured, it may be analysed for the unique clinical features it presents, however, generating an average of 2 (ideally 3) or more swallows per bolus condition, as was the standard of this study, provides a more dependable assessment of swallowing biomechanics. A total of 21 studies were excluded based on not meeting these criteria, across the two visits. These cases suggest that the child adequately tolerated the catheter in situ but had poor tolerance of the boluses offered. The reasons that led to an inability to achieve bolus trials predominantly related to refusal or rejection of standardised bolus types (saline or EFT Viscous), extensive frontal spillage i.e. spitting, or because syringe administration of minimum 2ml was refused and instead, 'individual sip' was recorded. While we implemented a minimum of 2 swallows per bolus condition and a minimum of 2ml volumes in our protocol, the majority of this cohort generated at least 3 swallows for analysis, and therefore the results predominantly represent averages of 3 swallows at 2 to 5ml volumes. Based on the children who provided swallows by sipping from a cup, it would be beneficial for future P-HRM-I research to specifically document age-related sip size in children, stratified also by medical condition. We also recognise that children with OPD may have difficulty containing the full volume administered to the oral cavity, and/or have difficulty initiating a swallowing response on command. Therefore, during P-HRM-I acquisition, we suggest that recording the intended bolus to be offered *and* any loss will assist in determining a more accurate indication of the bolus volume swallowed and later improve interpretation of swallowing biomechanics by bolus condition.

Additionally, we recommend that observation and documentation of the swallow initiation time following placement into the oral cavity will assist with later stage analysis and interpretation of results, as 'pocketing' is common in children. Chapter 7 further defines a method for

overcoming analysis in the event of piecemeal deglutition, which was prevalent throughout our paediatric investigations.

The benefits of tracking swallowing function over time are well recognised, however in the literature predominantly rely on patient reported outcome measures (317, 318). Despite the aforementioned challenges, we have demonstrated that P-HRM-I repeat data are obtainable in children, and it is expected that in a clinical context where results are likely to impact patient management, families would possibly undergo repeat P-HRM-I testing more readily. We also show that clinical interpretation of results can be optimised when bolus conductivity, bolus volume, and total swallow acquisition are standardised and appropriately managed.

9.4.2 Quantitative P-HRM-I data from Repeat Measurements

The recently outlined core outcome set of metrics by an international working group (191) has assisted with identifying reproducible parameters for comparison within- and between-patients and across centres and cohorts in the future. Further paediatric studies with larger cohort sizes are required to substantiate and confirm these findings, however we report paediatric P-HRM-I data to these international standards, for the first time here. Other novel P-HRM-I parameters are also presented.

9.4.2.1 Effect of Visit

The effect of visit across the two timepoints in this cohort did not significantly alter any of the swallowing metrics, even among children below 4 years age who experience rapid growth and development. The absence of changes seen in this cohort is most likely attributable to the stability of the underlying dysphagia aetiology in the small cohort examined. Overall, dysphagia status was particularly stable in this group and suggests that biomechanical features of swallowing remained largely unchanged across the 12- month period in these children all above 1 year of age. This is further verified by the FOIS status and DMSS of this group which generally remained unchanged across the 12- month period. We note one participant did shift FOIS status, this is discussed below.

9.4.2.2 Effect of Age Group

To further investigate changes in growth and development across childhood we compared differences in age groups, above and below 4 years of age. This showed that velopharyngeal contractility (VCI), UOS contractility post swallow (UOS CI), and the proximal oesophageal contractility (PCI) were significantly higher in older children, suggestive of larger anatomical structures, which are capable of generating greater contraction during bolus swallowing. UOS relaxation time was longer, and UOS distension pressure was also significantly greater in older children. These findings are generated from a broad dysphagia group with heterogeneous underlying medical conditions which may explain why select contractility of the pharynx is

affected. Some HRM metrics in the oesophagus have been shown to be dependent on child age and size, therefore adjustment for accurate diagnosis of oesophageal dysmotility disorders has been recommended (319). Despite the heterogeneous nature of this study cohort, age group effects have prevailed and therefore as P-HRM-I data accumulates in the paediatric sphere reference ranges specific for age and size will be required to more accurately interpret severity of pharyngeal and UOS dysfunction in children.

9.4.2.3 Effect of Medical Condition

Children with neurological diagnoses demonstrated significantly elevated pharyngeal contractility compared to the remainder of the cohort. Figure 9.4 above indicated the elevated velopharyngeal, mesopharyngeal, hypopharyngeal and composite pharyngeal contractile integral among children with a neurological diagnosis. These 4 children with spastic quadriplegic CP were physically impacted across Gross Motor Function Classification System (GMFCS) level IV and level GMFCS V. The GMFCS level of children with CP has recently been studied and showed that with increased severity of GMFCS level there was an increased chance of showing signs of OPD. Interestingly, the reported severity of OPD reduced with age from 79.7% prevalence at 18-24 months of age, to 43.3% prevalence at 60 months of age; however, for children most profoundly impacted with physical disability (GMFCS V), as is the case for 3 of 4 children in our study, higher prevalence of OPD symptoms is maintained (320). This is in line with the stability of OPD symptoms suggested in our study. Furthermore, when looking at these children with neurological diagnosis (mean age 9.25 years) we also see consistent Dysphagia Disorders Survey (DDS) scores across the 12-month period between visits 1 and 2. Malnutrition is, however, known to be common in children with spastic quadriplegic CP (321), and one patient required supplementary enteral tube feeding within the 12 month period, to reach weight targets, and elevate body mass index. This change affected FOIS scores in this subgroup of children with CP.

The biomechanical features of OPD in spastic CP have not been thoroughly described, however, spasticity is characterised by co-contraction of antagonist muscles and resistance to

the passive stretch of muscles which results in hypertonia (322). The elevated contractility measures we observe in this study confirm abnormally high force generation and suggest an inability to modulate amplitude of muscular activity within the swallowing mechanism. One recent paediatric study using electromyographical assessment also identified abnormally high suprahyoid musculature forces in these patients (322). However, to confirm our findings more rigorous investigation of the swallowing features specific to this group will be required in a larger cohort size. The remainder of the cohort here displayed GDD, or no established cause for OPD, and no condition-specific alterations to swallowing biomechanics were seen in either of these groups.

9.4.2.4 Effect of Viscosity

The effects of viscosity have not previously been reported in paediatric P-HRM-I data. Among the reliable measurements, unaffected by conductivity limitations, three metrics were altered by increasing viscosity. The UOS integrated relaxation pressure (UOSIRP) was increased, UOS basal pressure was reduced, and the distension contraction latency (DCL), an indicator of how well the bolus is propelled ahead of the pharyngeal stripping wave, was reduced with viscous compared to saline swallows. These findings each follow the expected pattern seen in healthy adult swallowing modulation reported in Chapter 6 and suggest that the patients in this OPD cohort demonstrated some ability to modulate and accommodate to altered bolus condition despite their dysphagia symptoms. Detailed interpretation of severity and extent of paediatric swallowing modulation capacity needs further investigation among homogeneous paediatric patient groups adjusted for age and size.

9.4.3 Conclusion

This study outlined our experience conducting P-HRM-I studies in children, has provided a proof of concept for performing repeat P-HRM-I assessments in children with OPD and investigated changes in swallowing biomechanics across two timepoints. While several factors influenced participants' return rate, we note that in general, repeat testing of HRM techniques

is obtainable in children with OPD and results can be optimised for clinical interpretation when protocols are standardised for bolus conductivity, bolus volume, and total swallows acquired per bolus condition.

The following Section 4, provides a full summary of all main effects studied in this research program, to demonstrate the overall context for the results generated in this research program, followed by a final discussion of main findings, future directions and thesis conclusion.

SECTION 4

This final section incorporates a thesis results summary with tables to demonstrate all main effects studied within the research program across adults and children. A final discussion of these findings summarises and contextualises the results from this research program within the current literature. Future directions are presented in line with the intended application of P-HRM-I methods going forwards, and following this, the thesis conclusion.

SECTION 4

Chapter 10:
Final Discussion, Future Directions and Thesis Conclusion

Thesis Results Summary

To summarise the key findings of this entire research program, all main effects observed across the P-HRM-I pressure flow parameters are presented in Summary Tables 9.2 and 9.3, below. The main findings shown across the suite of pharyngeal, UOS and proximal oesophageal pressure flow parameters, are colour-coded to indicate whether they support, contrast, or expand the current literature.

Table 9.2. ***P-HRM-I Patterns Observed During this Research Program in Healthy Adults***[13]

Patterns observed in P-HRM-I parameters in healthy adults											
Main Effect	***Novel Swallow Gateway findings contributing to current literature*** ***Supportive of previous manometry research*** ***Contrasting with previous manometry research***										
	Pharynx				**Upper Esophageal Sphincter**					**Esophagus**	**Global metric**
	Lumen Occlusive Pressure	**Hypopharyngeal Intrabolus Pressure**	**Bolus Presence Time**	**Distension-Contraction Latency**	**Pre-Swallow Pressure**	**Relaxation Pressure**	**Opening Admittance**	**Post-Swallow Pressure**	**Relaxation Time**	**Proximal Esophageal Contractility**	**Swallow Risk Index**
Bolus volume	↑ with vol.	↑ with vol.	↑ with vol.	↑ with vol.		↑ with vol.	↑ with vol.	↑ with vol.	↑ with vol.	↑ with vol.	↑ with vol.
Bolus consistency		↑ with cons	↓ with cons.	↓ with cons.	↓ with cons.	↑ with cons.	↑ with cons.	↓ with cons.	↓ with cons.	↑ with cons.	↑ with cons.
Catheter diameter					↑ with diam.	↑ with diam.		↑ with diam.	↓ with diam.		
Age (18 – 80yrs)	↓ with age					↑ with age	↓ with age	↑ with age			↑ with age

Note. This table demonstrates the pressure flow parameters studied in healthy adults according to the main effects of bolus volume, bolus consistency, and catheter diameter. Referenced literature is included in the footnote and is referred to in the final discussion (age effects are included in the table only). The arrows ↑↓ indicate direction of effect on the metric class, and no arrow indicates no significant effect. These findings illustrate a novel contribution (blue), whether they align with previous literature (green) or contrast previous literature (orange). Blue metric subheadings indicate novel parameters generated with Swallow Gateway™ analysis. Secondary effects of age and gender are included. Statistical significance can be referred to in Chapters 5 and 6.

[13] Bolus volume: 151, 157, 168, 197, 245, 284, 326

Bolus consistency: 168, 192, 198, 212, 219, 283, 284, 285, 324, 327

Catheter diameter: 148, 192, 236, 257, 264, 265, 266, 324, 325

Age (18-80 yrs): 282

Table 9.3. ***P-HRM-I Patterns Observed During this Research Program in Children***[14]

Patterns observed in P-HRM-I parameters in children												
Main Effect		*Novel Swallow Gateway findings contributing to current literature* *Metrics excluded from analysis due to bolus conductivity limitations* *Findings supportive of previous manometry research* *Contrasting with previous manometry research* *- if not reported*										
		Pharynx				**Upper Esophageal Sphincter**					**Esophagus**	**Global metric**
		Lumen Occlusive Pressure	**Hypopharyngeal Intrabolus Pressure**	**Bolus Presence Time**	**Distension-Contraction Latency**	**Pre-Swallow Pressure**	**Relaxation Pressure**	**Opening Admittance**	**Post-Swallow Pressure**	**Relaxation Time**	**Proximal Esophageal Contractility**	**Swallow Risk Index**
Piecemeal deglutition (PD)/ bolus volume		↑ with less PD			↑ with less PD		↓ with less PD	↑ with less PD		↑ with less PD	-	-
Age group	**<1y vs. 1-4 y**	↓ with age	↑ with age	-	↑ with age		↓ with age	↑ with age			-	-
	0-4y vs. 5-18y	↑ with age					↓ with age			↑ with age	↑ with age	
Bolus consistency					↓ with cons.	↓ with cons.	↑ with cons.					
Medical condition		↑ with spasticity										
Repeat visit												
OPD vs. controls				↑ with OPD		-	↑ with OPD		-	-	-	↑ with OPD
With vs. without overt clinical signs of OPD					↓ with signs	-	↑ with signs	↓ with signs	-	-	-	↑ with signs

Note. This table demonstrates the pressure flow parameters studied in children according to the main effects shown above. The arrows ↑↓ indicate direction of effect on the metric class, and no arrow indicates no significant effect. Referenced literature is included in the footnote and is referred to in the final discussion. These findings illustrate a novel contribution (blue), whether they align with previous literature (green) or contrast previous literature (orange). Metrics excluded from analysis due to bolus conductivity issues are coded in grey. Un-coded dashed boxes represent metrics which were not reported. Blue metric subheadings indicate novel parameters generated with Swallow Gateway™ analysis. The statistical significance of each effect can be referred to in Chapters 7-9.

[14] OPD vs. controls: 185
With or without signs of OPD: 185

Chapter 10: Final Discussion

This thesis demonstrates that P-HRM-I methods comprehensively characterise pharyngeal swallowing physiology and pathophysiology according to contractility, distension, and bolus flow timing events. Important insights into healthy pharyngeal neuromodulation have deepened our understanding of the value and application of P-HRM-I as an instrumental swallowing assessment (Chapters 5 and 6). Additionally, the paediatric studies demonstrate evidence for the application and repeat testing of pressure flow parameters in children (Chapters 8 and 9), highlighting necessary considerations when performing and interpreting results from paediatric tests (Chapters 7 and 9). This final discussion summarises and contextualises the key outcomes of this thesis, in relation to the current literature, and proposes the clinical contexts and potential added value P-HRM-I may offer future researchers and clinicians. Altogether, the swallowing observations described in this thesis may bring P-HRM-I methods a step closer towards clinical application, which, in light of the increasing prevalence of paediatric OPD (1-4) may one day serve to enhance diagnostic accuracy and develop targeted therapies according to swallowing biomechanical dysfunction.

10.1 The Effect of Catheter Diameter on Luminal Pressure Readings

The healthy adult study presented in Chapter 5 contributes a significant finding to the HRM literature, outlining the importance of interpreting all pressure results in the context of catheter specifications. This study demonstrated that UOS contractility measurements pre- and post-swallow, as well as UOS relaxation pressures, were elevated with a larger diameter catheter. This can be explained by length-tension properties of luminal muscles, a phenomenon that has previously been observed and described in the context of manometric assessments (263-265). According to this principle, pharyngeal contractile pressures were expected to differ with catheter diameter, however, only a statistical trend for increased pressure ($p<0.077$) was observed with a wider catheter. This may reflect the potential variability in measuring

pharyngeal peak pressures compared to pharyngeal contractile integrals (i.e. PhCI, VCI, MCI and HPCI), the latter of which are proving to be more reliable measurements of pharyngeal lumen occlusive pressures (147, 191, 235, 256, 323, 324). Therefore, the data presented in Chapter 5 suggest that future studies should compare catheter diameter effects on pharyngeal contractile integrals to further establish any potential alterations to pharyngeal contractility according to catheter diameter.

Overall, the findings from this research emphasise the need for diagnostic reference ranges specific to catheter specifications for reliable clinical analysis and accurate interpretation of HRM data. Chapter 6 provides a benchmark for healthy pressure flow parameters, as acquired with an 8Fr unidirectional catheter. As would be expected, direct extrapolation of these adult P-HRM-I reference ranges is not appropriate for the paediatric setting due to anatomical and size differences between adults and children. However, in the absence of true healthy paediatric reference ranges, the findings presented in Chapter 6 provide a guideline for what to expect in the healthy swallow system in general, and therefore may assist with initial interpretation of paediatric P-HRM-I studies.

10.2 Healthy Swallowing and the Effects of Bolus Volume and Viscosity

The reason for testing different bolus conditions in healthy adults is twofold: i) to quantify the typical capacity of the pharyngeal swallowing system to accommodate increased bolus sizes and textures and ii) to measure the typical alterations in the swallowing mechanism when bolus characteristics are modified, as therapeutic bolus modifications are frequently implemented in people with OPD. For this purpose, healthy swallowing was comprehensively evaluated in adults (in Chapters 5 and 6) in response to a range of altered bolus volumes and viscosities. Our results illustrate that P-HRM-I methods capture the intricate biomechanical adaptations of swallowing modulation in relation to pharyngeal and UOS contractility, distension and bolus flow timing.

10.2.1 Bolus Volume

The bolus volume findings in this thesis are in line with previous manometry research (150, 156, 167, 196, 244, 283, 325), supporting the notion that anticipatory UOS basal pressures are unaffected by altered volume, but pharyngeal, UOS and proximal oesophageal deglutitive pressures increase with larger bolus volumes. Furthermore, UOS relaxation, UOS opening extent and pharyngeal distension pressures were particularly sensitive in detecting the swallow responses required to accommodate volume changes, especially with increases up to 20ml. Establishing these biomechanical changes that occur when the pharynx and UOS are challenged with increased bolus volumes characterises the swallowing physiology involved, confirms and contributes to what is known of the swallowing modulation mechanism and provides a benchmark against which to interpret OPD. Therefore, challenging the swallowing mechanism with increased bolus volumes in P-HRM-I assessments will likely indicate the thresholds at which compensatory behaviours such as piecemeal deglutition (183, 304) emerge in OPD patients. In turn, this has the potential to reveal the pathophysiology which leads to these behaviours. Similarly, the therapeutic benefit of implementing smaller volumes may be tested in relation to presenting pathophysiology.

10.2.2 Bolus Viscosity

Similar to bolus volume, the overall effects of increasing bolus viscosity levels in this research echoes previous reports of associated elevated hypopharyngeal intra-bolus pressure (326), elevated UOS integrated relaxation pressures (IRP) (167, 326), reduced UOS pre-deglutitive pressure (284), and reduced post swallow pressures (167, 284). In contrast to the effects of bolus volume, increased bolus viscosity led to reduced UOS basal pressure and relaxation time, which were the most sensitive markers of the swallowing response to thicker boluses. In other words, thinner boluses led to elevated UOS basal pressure pre-swallow, a phenomenon which may reflect a vagal-mediated protective mechanism aimed to assist with the generation of sub-atmospheric pressures in the proximal oesophagus. This results in a larger pressure

gradient change upon UOS opening, creating a greater suction effect on a thinner, faster moving bolus as it passes the airway. In line with this notion and previous research (197, 211, 218), negative nadir UOS relaxation pressures were observed, particularly across thinner bolus viscosity levels.

Interestingly, there is some contention as to whether thicker bolus viscosities modify pharyngeal contractility measures in the healthy adult swallow. Some studies report no changes in pharyngeal measures (283, 326), others report reduced pharyngeal swallowing pressures during thicker viscosities (284, 323) and one study showed elevated hypopharyngeal peak pressures with increased viscosity (282). The findings in this thesis align with those studies that did not report any changes to pharyngeal contractility. However, a recent review of the literature combining patient and healthy volunteer groups has described an increase in pharyngeal pressures and hypopharyngeal intra-bolus pressures with thicker bolus consistencies (191). Despite these discrepancies, the comprehensive dataset presented in this thesis from a substantial sample size of healthy volunteers and inclusion of a broader than previously studied range of volume and viscosity levels provides dependable descriptions of swallowing modulation. Thus, it is proposed that this dataset may be utilised as a reference for interpretation of 8Fr catheter acquired studies in patients with OPD.

10.2.2.1 Effect of Bolus Viscosity in Children with OPD

The effects of bolus viscosity on P-HRM-I parameters appear not to have been previously reported in paediatrics, despite the widespread therapeutic implementation of feed thickeners to reduce aspiration risk (327). The research presented in Chapter 9 enabled some investigation into the effects of bolus viscosity on paediatric OPD swallowing and showed that greater bolus viscosity led to increased UOS relaxation pressures, reduced UOS basal pressure and shortened pharyngeal DCL. These results mirror the effects of increased bolus viscosity seen in the healthy adult data and suggest a level of preserved swallow modulation capacity, despite the symptoms of OPD in this small paediatric cohort we studied. Future studies should quantify paediatric swallowing modulation more comprehensively, particularly

regarding therapeutically thickened boluses and adjusted bolus flow methods, explained further in the Future Directions section below.

10.2.3 Bolus Flow Timing Measures

In light of the reported findings in healthy adults, bolus flow timing measures were significantly altered with modifications to bolus volumes and viscosity levels (as outlined in Chapter 6). In general, the clinical value of the timing measures relates to the ability to detect the interaction of bolus flow and contractility of the pharynx and UOS. The BPT metric is usually significantly prolonged in patients compared to controls (54, 184, 239), indicating a delayed pharyngeal swallow response associated with OPD. A shorter DCL is usually indicative of greater dysfunction and incoordination, suggesting the bolus is not adequately propelled ahead of the pharyngeal stripping wave. The a short DCL was originally shown to correlate with pre-swallow pharyngeal bolus presence (239) (i.e. premature spillage on radiology) and continues to flag OPD in various patient populations such as in relation to post obstructive sleep apnoea surgery (250), and in paediatric OPD of broad aetiology (54).

In the healthy adult research, bolus flow timing measures showed opposite responses to altered bolus volume and altered bolus viscosity. Increased bolus volumes led to prolonged BPT, DCL, and UOS RT, and increased bolus viscosity led to the shortening of these timing metrics. Shorter timing metrics associated with thicker bolus viscosity, relative to thin liquids is somewhat intuitive. A thicker bolus flows more slowly and therefore 'arrives' later in the pharyngeal swallow sequence compared to a thin liquid that flows more quickly and therefore arrives relatively earlier. As such, thicker liquids (when compared to thin liquid) result in reduced BPT and DCL as the bolus arrival time and the pharyngeal contraction time are closer together, and the necessary duration of UOS relaxation to accommodate a slower moving thicker bolus is shorter. In contrast, pharyngeal BPT, DCL and UOS RT were all prolonged with larger bolus volumes, which is equally intuitive, in that a larger bolus volume has greater velocity (243) and therefore is thought to arrive relatively earlier in the swallow sequence compared to a smaller bolus volume. An increased UOS RT is a well-established observation of larger bolus volumes

(94, 103, 148, 162, 178, 217, 220), as is reduced UOS RT with thicker boluses, as previously reported (220). These substantially altered timing measurements by bolus condition emphasise the intricate adaptations required of the swallowing mechanism to accommodate bolus characteristics and optimise bolus passage and airway protection in the healthy pharyngeal swallowing system (178, 195). These typical responses expressed within the bolus flow timing measures are important considerations for the interpretation of swallowing efficiency of bolus transfer in patients with OPD.

Altogether, these results describe the complex biomechanical features occurring during swallowing modulation, and this research has contributed to the confirmation and further characterisation of swallowing features by P-HRM-I pressure flow parameters. Future studies should further clarify the effects of bolus conditions on healthy swallowing in line with the recently established core outcome set metrics (191).

Swallowing biomechanical features in patient groups detected with P-HRM-I have been described predominantly in adult populations, however paediatric pharyngeal manometry studies are increasingly emerging in the literature (54, 144, 169, 183, 184, 235, 254, 328). The findings from this research program (presented in Chapters 7 to 9) contribute important new descriptions of swallowing biomechanics from integrated pressure *impedance* technology in older infants and children with OPD. In particular, the impact of age group emerged as a key effect on swallowing function in childhood and is discussed below.

10.3 Paediatric Findings According to Age Group

Age had a significant effect on pharyngeal contractility pressures, most likely relating to the rapidly changing anatomical structures occurring throughout early childhood. These effects were particularly evident in the early years of childhood as demonstrated within a homogeneous cohort of children without overt signs of OPD, investigated primarily for oesophageal motility post trache-oesophageal fistula repair, and studied in Chapter 7 in relation

to piecemeal deglutition. This study showed, in infants 5 months to 1 year of age, pharyngeal pressures and hypopharyngeal IBP were higher, UOS opening extent was greater and UOS relaxation pressure was lower compared to children 1-4 years of age. These findings align with a previous report of higher than expected pharyngeal pressures found in infants (169). A likely explanation for this phenomenon is the smaller pharyngeal chamber size in babies and the prolonged contraction of their pharyngeal luminal muscles in the presence of the recording (HRM/P-HRM-I) catheter (263-265). While this may suggest a direct catheter effect on swallowing physiology, unfortunately this is unpreventable as these biomechanical measurements cannot be acquired without intra-pharyngeal presence of the catheter. If future studies can generate data in larger cohorts stratified by age group, this may further substantiate these age-related findings and provide reference ranges relative to anatomical differences throughout childhood. Additionally, the continued reporting of standardised P-HRM-I outcomes with age-related reference ranges stratified according to medical condition may help to overcome concerns of the impact of the catheter in situ on swallowing function.

This research also showed age related effects in children above 5 years who demonstrated greater pharyngeal pressures, and reduced UOS relaxation pressures compared to younger children (1-4 years of age). This is intuitive, as older children are expected to generate greater pressures with larger, stronger musculature. Likewise, reduced relaxation pressures likely relate to wider luminal distension of the UOS during relaxation compared to smaller children. Interestingly, the duration and magnitude of swallowing musculature activity has been studied with submental electromyography (EMG) and showed that by 5 years of age, children demonstrate ‘adultlike control’ (329), which supports our manometry findings in this age group. Similarly, bolus flow timing measures, UOS relaxation time and DCL increased with age and likely reflect the ability for larger pharyngeal and UOS structures to accommodate larger bolus volumes leading to prolonged bolus distension time through the pharynx and UOS. Altogether, the age group effects on manometric recordings demonstrate the swallowing biomechanical changes occurring throughout childhood and reinforce the need for developmental age group

specific reference standards in the paediatric setting. P-HRM-I normative reference ranges are not readily achievable in children due to ethical concerns with conducting invasive manometry procedures in healthy children. However, a possible means to acquire such data would be for future studies to acquire surrogate pharyngeal control data from oesophageal investigations, as was accomplished in our research presented in Chapter 8. It is acknowledged that pharyngeal swallowing function can be indirectly impacted in some conditions of oesophageal dysmotility, therefore careful consideration of inclusion of participants in such a project is necessary.

Overall, the paediatric studies in this thesis have shown that age effects on pressure flow parameters are evident between infants and young children, and between young children and older children. Therefore, age is a particularly important consideration when interpreting paediatric pharyngeal manometric results. In addition to age, the presence of piecemeal deglutition during P-HRM-I analysis is another important consideration. The study presented in Chapter 7 investigated the prevalence of piecemeal deglutition (PD) in a paediatric dataset and demonstrates an approach for PD evaluation during P-HRM-I swallow analysis, as described below.

10.4 Paediatric Findings According to Piecemeal Deglutition

This research demonstrated that PD is a phenomenon that significantly impacts P-HRM-I parameters, in particular because portioning significantly affects the bolus size of each swallow in a PD sequence (304). Additionally, when a swallow sequence occurs following administration of a test bolus it is difficult to ascertain PD from other possible swallow sequence categories, namely secondary dry, preceding dry, and clearing swallows (330). These additional swallow sequence categories all appear as PD unless the bolus-carrying swallows can be objectively identified. Therefore, careful consideration of swallow selection from a topographically displayed swallow sequence is needed to optimise analysis and best represent swallowing function. In Chapter 7 an approach was developed that utilises embedded

impedance data, indicated by admittance curves, to guide swallow selection for analysis. Specifically, the assessor uses the admittance curves to track bolus-carrying swallows and differentiate these from secretion or non-bolus swallows. The peak of each admittance curve, and the associated admittance value, guides the assessor in selecting the '*dominant*' or largest bolus carrying swallow for analysis. In this study *dominant* swallows showed greatest statistical confidence for main effects compared to averaged data of all swallows within a piecemeal sequence. To date, the first swallow in a swallow sequence is predominantly relied upon for analysis. However, this may not optimally represent an individual's bolus swallow function. We therefore recommend selection of the largest bolus carrying swallow (the dominant swallow), guided by impedance/admittance curves, as the most reliable choice for analysis. Along with improving the reliability of the pressure flow parameters and the statistical confidence of the main effects, selecting the dominant swallow saves time compared to averaging all swallows in a piecemeal sequence, and therefore proves a clinically convenient outcome.

While the impact of PD on P-HRM-I is a novel contribution to the literature, particularly in children, the impact on the swallowing metrics observed in Chapter 7 aligns with previous reports within this research (Chapters 5 and 6) and that of others (150, 156, 167, 196, 244, 283, 325) in relation to the pharyngeal response to larger bolus volumes. Specifically, we found that *dominant* swallows from smaller piecemeal sequences caused greater pharyngeal contractility, increased UOS opening extent, prolonged UOS relaxation time, and prolonged pharyngeal DCL. This is intuitive, as with fewer swallows in a piecemeal sequence the bolus volume is likely to be larger, thus reflecting the pharyngeal and UOS modifications seen with larger bolus volumes in healthy swallowing. Further investigation of the volumes which achieve single swallows at different age groups is warranted.

One discrepancy within the PD study in Chapter 7 was that the UOS relaxation pressure metric reduced for averaged PD data but increased according to the dominant swallows from fewer PD swallow sequences. This may be because the UOS relaxation pressures for smaller bolus volumes across the averaged piecemeal sequences would have reduced the overall UOS

relaxation pressure value, compared to the UOS relaxation pressure taken from the largest bolus volume, which is expected to be higher. Despite this variation, the dominant swallow from a PD sequence is recommended for use when interpreting UOS relaxation pressure due to the improved reliability and biomechanical relevance of using a larger bolus volume for evaluation.

10.5 Paediatric Findings According to Overt Signs of OPD and Medical Condition

The intention behind the use of P-HRM-I parameters to characterise swallowing features associated with overt signs of OPD (see Chapter 8) and specific medical conditions (see Chapter 9), is to enhance our understanding of the pathophysiological features observed in children. In the future, this may improve diagnostic specificity and treatment options for children with OPD. The sensitivity of various clinical signs and symptoms of paediatric OPD has been tested by Weir and colleagues, revealing that wet voice, wet breathing and cough significantly associate with aspiration of thin liquids (331). Additionally, in that study, cough was found to be associated with post swallow residue (331). These are important reports which support the use of clinical measures studied in this research program. The study by Weir and colleagues, also highlighted clinical OPD symptoms according to patient age and medical condition, demonstrating that cough is less reliable in children below 1 year of age and among children with neurological disability. This reiterates the need for future studies to generate age and medical condition specific data in paediatric populations. The P-HRM-I parameters observed in this research program are presented below in the following order: pharyngeal contractility, UOS measurements, bolus flow timing measures and the SRI, for which we demonstrate a paediatric specific cut-off value.

10.5.1.1 Pharyngeal Contractility Measures

Measuring pharyngeal contractility with manometry techniques has attracted clinical and research interest due to the ability to quantify pharyngeal vigour of the stripping wave. Previous literature has predominantly focused on acquisition of *peak pressures* which are easy to

generate during analysis. In the study described in Chapter 8, paediatric pharyngeal vigour was detected as peak pressures, which did not significantly differ between patients with OPD (of broad aetiology) and controls, nor did it differentiate patients with and without overt clinical signs of OPD (i.e., cough, wet voice, wet breath sounds and multiple swallowing).

The non-discriminating pharyngeal pressure results in Chapter 8 are in line with another paediatric P-HRM-I study which showed no change in pharyngeal contractility, also measured as peak pressure, in a cohort of broad OPD aetiology and aspiration evidence on radiology (184). Additionally, pharyngeal vigour remained unchanged in a case series report of high-resolution videomanometry in children with velocardial facial syndrome (VCFS) (254). One study in infants with OPD showed significantly elevated pharyngeal peak pressures, although it was proposed that the 3.6 mm diameter catheter relative to the small pharyngeal spaces in infants contributed to this result (169). In adult patients, pharyngeal peak pressure has been reported as a non-specific correlate of symptoms of OPD (153, 250). Overall, the current descriptions of paediatric pharyngeal vigour are limited to a few studies in children with broad medical aetiology (54, 169, 184, 328), a single study of VCFS (254), two studies of prematurity (144, 235), and the contributions of this thesis (54, 183). Additionally, the variations in reports are likely a result of the small, mostly heterogeneous cohorts and differences in acquisition methods (e.g. pressure sensor arrays; catheter diameters). The overall lack of a significant relationship with clinical symptoms most likely relates to acquisition of peak pressures rather than contractile integrals. However, pharyngeal *contractile integrals* provide a measure of pressure over space and time, and more recently are proving to enhance recording accuracy of sustained pressures, especially within the velopharyngeal and mesopharyngeal regions (191). Acknowledging that contractile integrals are proving to be more specific at detecting the intricate dynamics occurring in each pharyngeal region (191), future research should study contractile integrals in larger, ideally homogeneous cohorts to substantiate and clarify the paediatric pharyngeal contractility literature. In accordance with the advancements of the

pressure flow parameters utilised and studied in this research program, Chapter 9 reports pharyngeal contractility integrals in the paediatric cohort of repeat P-HRM-I tests.

Regarding medical condition, this study showed altered pharyngeal contractile integrals in a subgroup of children with spastic quadriplegic CP, understood to be the first manometric description of swallowing in this patient group. These children demonstrated increased pharyngeal contractility, a relatively uncommon finding that ordinarily would require prompt further investigation, particularly in patients without an established neurological diagnosis (59). However, in these children known to have hypertonia and muscle spasticity (322), elevated pharyngeal contractility was expected. As this was a small sub-group of only 4 children, a more extensive investigation in a larger cohort of children with CP is needed to substantiate these findings and may produce more comprehensive outcomes across other contractility, distension and bolus flow timing parameters. This preliminary finding is small but significant, as it has highlighted key pathophysiology using quantitative parameters specific to a homogeneous medical condition sub-group.

10.5.1.2 Upper Oesophageal Sphincter Measurements

The study of children with OPD (Chapter 8) provided important insights into the pathophysiology of paediatric OPD in the context of UOS dysfunction. In particular UOS resistance and reduced opening extent were observed. These findings are in line with a previous paediatric P-HRM-I study, which also showed UOS pathophysiology as a key feature of dysfunction in children with evidence of aspiration seen on VFSS (184). Significantly elevated UOS relaxation pressure was observed in both studies. In the research presented in this thesis, elevated UOS relaxation pressure differentiated children with OPD from controls, and among children with OPD differences were detected for children with overt symptoms (such as cough, and wet voice quality), compared to those without. Quantifying UOS relaxation and UOS opening extent is a key advantage of P-HRM-I methods over VFSS and FEES, which rely on visual and kinematic analysis of swallowing physiology. Additionally, it is critical to define reliable UOS function measures, as UOS restriction obstructs bolus flow and contributes to

compromised airway protection as the bolus is forced towards the larynx. Abnormal UOS relaxation has previously been reported in children with OPD symptoms. Children with VCFS with associated symptoms of gagging, profuse oral secretions, nasal regurgitation and aspiration have demonstrated reduced UOS relaxation (254). Additionally, in relation to neurodevelopment of premature infants, increased UOS relaxation pressures are significantly improved and reportedly appear to reach nadir more appropriately beyond 31 weeks gestational age (144). Furthermore, neurologically vulnerable neonates have been shown to have increased excitatory output to the UOS, characterised by greater UOS resting pressure and a more sensitive response to UOS stimuli compared to healthy infants (332). To indicate pathology of the UOS, a case example is presented in Appendix 5 demonstrating cricopharyngeal achalasia in a five-month-old boy requiring cricopharyngeal muscle botox therapy guided by P-HRM-I assessment. While it is an unusual condition of childhood, cricopharyngeal achalasia causes severe UOS obstruction and usually requires manometry techniques to guide the required therapeutic intervention options of botox therapy, dilatation or myotomy, depending on centre protocols and the child's age and severity of the condition (252, 253, 333-337). These UOS-specific findings across paediatric age groups and medical conditions demonstrate the impact of UOS pathophysiology in children, and its contribution towards OPD symptoms should not be underestimated. Therefore, UOS physiology should be considered in all cases of paediatric OPD assessment. It is thought that UOS basal pressures may assist in the differentiation of patients with co-occurring oesophageal causes of UOS dysfunction, such as GORD, where elevated UOS basal pressures may be present. UOS basal pressure should be investigated in future OPD studies, with and without co-occurring oesophageal conditions.

10.5.1.3 Effortful Swallowing Practice and Raised UOS Relaxation Pressures: A Case Example

When conducting the research presented in Chapter 8 we studied a female participant with benign myoclonus of infancy, a history of aspiration pneumonia, and ongoing OPD symptoms

at 7 years of age. This participant was practising effortful swallowing with the clinical rationale to increase pharyngeal contractility to overcome the pharyngeal residue visualised on VFSS. Effortful swallowing is a frequently recommended swallowing strategy (187), however in this case, the P-HRM-I assessment and analysis of swallowing revealed vastly elevated UOS relaxation pressures during effortful swallowing compared to natural bolus swallowing. This increased UOS resistance was hypothesised to exacerbate UOS dysfunction, potentially leading to increased pharyngeal residue and worsened symptoms, as reduced UOS opening extent and relaxation time has been shown to result in increased pharyngeal residue (190, 193, 338). This case example demonstrates the ability of P-HRM-I to detect subtle swallowing biomechanics that are difficult to identify on VFSS, enabling a tailored therapeutic approach for optimal and individualised outcomes. In this case, feedback regarding parameters observed during regular and effortful swallowing conditions was provided in report format to managing clinicians, unfortunately the outcomes of ongoing management for this patient were unavailable for report here. Manometry methods may be employed in future paediatric investigations of swallowing manoeuvres to gain this information, as seen in some adult contexts (200, 324, 339, 340). Additionally, successful implementation of swallowing manoeuvres by adult patients using pressure topography colour plots as biofeedback has been reported (290) and treatment types and practice frequency have been identified as important considerations to measure (341). These studies show the potential to use manometric biofeedback to promote learning of swallowing skills and may be implemented in the paediatric setting to improve and optimise therapeutic swallowing strategies.

10.5.1.4 Bolus Flow Timing Measures in Children with OPD

In the paediatric data presented in this thesis, bolus flow timing measures of BPT, DCL and UOS RT were affected most significantly. A prolonged BPT differentiated children with OPD compared to controls, confirming previous reports of a longer pharyngeal bolus flow interval when aspiration is evident on VFSS (184, 204). In line with the effects of increased bolus volume, DCL was longer in children who displayed fewer piecemeal swallows in a pattern, and

DCL was shorter with increased viscosity. These findings mirror the observations seen in healthy adult modulation to changes in bolus volume and viscosity (in Chapter 5), suggesting the paediatric patients we studied retained at least some ability to modulate their swallowing mechanism to changing bolus conditions. Age group had a significant effect on bolus flow timing measures: increased DCL and UOS RT were observed in children above 4 years of age, compared to children below 4 years of age. This is likely related to larger pharyngeal chamber size in older children who are capable of swallowing relatively larger volumes, and larger volumes lead to prolonged temporal measurements of bolus flow through the pharynx and UOS. In general, bolus flow timing measures may be clinically valuable during the description of bolus transport efficiency, enhancing overall characterisation of swallowing biomechanics if interpreted in the context of the contractility and distension characteristics of a patient's swallow.

10.5.1.5 The Swallow Risk Index

The final pressure flow metric studied in this thesis is a global measure of OPD, the SRI. An SRI cut-off value of 15 to identify aspiration risk has been tested and evidenced in adult patients with OPD of broad aetiology (59, 153, 236) and in the critically ill (276). Values ≥15 indicate increasing OPD predisposing to aspiration. The healthy adult data reported in Chapter 6 showed the SRI remained sub clinical i.e., below 15, however, increased with the challenges of increased bolus volume and viscosity levels. The elevated SRI in these healthy adults reinforces the increased 'load' to the swallowing mechanism in the context of larger bolus volumes, such as 20ml. This concept of increased load may be utilised in assessments of patients with OPD, detected at lower thresholds when the volume or viscosity level exceeds the competence of a patient's swallowing mechanism. In our paediatric data, children with greater severity of OPD symptoms presented with greater dysfunction of swallowing pathophysiology and this was specifically reflected by an increased SRI. The healthy controls included in the study reported in Chapter 8, without clinical signs or reports of OPD, enabled a paediatric-specific cut-off point ≥8 to be defined. This demonstrates that the SRI has adequate

sensitivity to detect alterations within the swallowing mechanism of healthy adults, adult patients, and paediatric patients. Particularly, the distinct paediatric cut-off point ≥8 restates the requirement for paediatric-specific reference ranges moving forwards.

Altogether, the biomechanical outcomes from the data in this thesis have advanced the characterisation of paediatric OPD pathophysiology according to parameters of contractility, distension, and bolus flow timing. These paediatric findings also offer important insights into the potential clinical use of these measurements. There are several contexts where quantitative baseline and repeat measurements of swallowing physiology would optimise the effectiveness of a child's OPD management. These contexts include: children with evolving or degenerative medical conditions; children with persistent adverse outcomes such as lung disease and nutritional deficiencies which prevail despite dietary modifications and therapeutic strategies; and children requiring surgical interventions, e.g. pre- and post-dilatation or botox therapy in cricopharyngeal achalasia. Although the application of manometry in paediatric case studies of cricopharyngeal achalasia has been reported (336, 337), ongoing quantification of these measurements in future paediatric research will confirm these findings and continue the development of diagnostic frameworks for interpretation of a broader range of clinical presentations. Several considerations for application of manometry methods in children were revealed in Chapter 9 and are discussed below.

10.6 Lessons Learned from Conducting Paediatric P-HRM-I Studies in Children

With a range of promising contexts for the application of paediatric P-HRM-I, exploration of the factors that influence feasibility and successful performance of P-HRM-I procedures in children was critical. The unique challenges that arose in our experience related to: i) age appropriate avoidance behaviours such as crying, head turning and excessive movements; ii) refusal to receive and/or swallow bolus media; iii) frontal spillage of the orally administered bolus related

to spitting or poor oral control; and iv) pocketing the bolus orally with excessive delay in swallow response due to the unpalatable taste of saline and/or as an avoidance strategy. In summary, our research showed that data quality of P-HRM-I studies was heavily influenced by poor tolerance, refusal to swallow, and insufficient bolus volumes and/or swallow total per study (as outlined in Chapter 9). Additionally, return rate for repeat tests was heavily influenced by avoidance of hospital attendance purely for research purposes. Despite these factors which limited the quality of P-HRM-I recordings and return rate in children, our research shows quality data and repeat studies can be obtained. Recognising P-HRM-I has the potential to enhance OPD assessment, warrants a range of efforts to be made to overcome the unique challenges faced when performing manometry procedures in children. Suitability for the P-HRM-I procedure is a primary consideration and is discussed below.

10.6.1 Patient Age and Study Tolerance

Our research showed that ascertaining a child's suitability for a manometry test is necessary to optimise test tolerance. Poor tolerance limits the value of a P-HRM-I study and may contribute to avoidance of repeat testing in some children in the future. Patient age was a key contributor to test tolerance in our research. Half of the children studied, below 4 years of age tolerated the study poorly as indicated by excessive crying and refusal to receive boluses. This suggests approximately a 50% chance of obtaining an analysable study in this age group, however it is important to note the youngest child we studied was seven months old. We expect improved tolerance would be likely in infants below seven months of age as there is evidence of manometry studies performed by other research groups in pre-term and young infants (220, 222, 235, 342, 343) suggesting success in application of these methods in early infancy. In our research, tolerance and data quality were vastly improved in children above 4 years of age. For this reason, researchers and clinicians are urged to consider the likely success of a study based on a child's age, in combination with its potential benefits to ongoing management and interventions. Children with severe oral aversions and hypersensitivities may experience added difficulty, therefore we recommend taking this into account when ascertaining a child's

readiness for undergoing the procedure. Ultimately, clinical discretion should determine the cost/benefit of conducting a manometry study in any child.

10.6.2 Influence of Environmental Factors

In Chapter 9, part 9.3.1.1, strategies to encourage a calm environment are outlined as a means of optimising study outcomes in children. These strategies relate to softer room lighting, avoiding loud noises and limiting distractions which may overstimulate a child. These methods were implemented according to the principles employed by many NICUs to optimise well-being of infants in high sensory stimuli environments (344). Trials of hypnotherapy techniques, which anecdotally benefited patients in our study, have proven successful in reducing distress during medical procedures (345-347) and may be tested in future manometry studies for their ability to further reduce stress and movement artefact associated with poor test tolerance. Other avenues to promote engagement and preparation for manometry studies may be explored, such as the development of social stories, which aim to prepare children and improve predictability of what to expect from unfamiliar experiences such as hospital visits (348). Altogether, these recommended strategies aim to improve the manometry experience and subsequently optimise tolerance and data quality.

10.6.3 The Role of Test Bolus Properties

Along with ensuring a child's suitability for the test, and implementation of strategies to optimise study tolerance, P-HRM-I data quality hinges heavily on the conductivity of boluses offered. Bolus conductivity ensures impedance/admittance values generate reliable distension and bolus flow timing measures. Acceptance of optimally conductive boluses is challenging in children who frequently display fussy tendencies, particularly to unfamiliar products such as saline. Standardised products such as apple flavoured SBMkit™ may improve bolus acceptance, safeguard against bolus conductivity issues and ensure measurement reliability when compared over time and between cohorts. Several children in our research declined the saline and fruit flavoured EFT Viscous boluses included in the study protocol, instead choosing

home-brought options such as chocolate milk or juice. These products with unstandardised conductivity properties were excluded from our final dataset to ensure research rigor, however there may be scope to standardise the conductivity and viscosity properties of a wider range of test boluses offered to children in future research and clinical studies.

10.6.4 Clear Roles and Responsibilities Facilitate Efficiency of Study Acquisition

A streamlined approach aids in the outcomes of the P-HRM-I procedure, which can be conducted in a timely manner, ensuring children and their families are engaged and their needs are accommodated throughout the process. The P-HRM-I procedure involves careful preparation of bolus products, catheter cleaning, catheter configuration and calibration (outlined in the overview of methods described in Chapter 4), and communication with families to schedule appointments (see Appendix 8). Efficient processes were achieved by clearly defined roles and responsibilities of each team member (research nurse, SP and scientist) in relation to the study preparations and P-HRM-I recordings. It should be noted that the trained and experienced research nurse was solely responsible for catheter placements and remained present throughout all studies to observe and care for the medical needs of each child.

Overall, we have presented a range of factors to consider when implementing manometry assessments in children, to optimise the acquisition of analysable data and interpretation of the results. These factors have spanned the age and suitability of a child for the manometry test based on their likelihood to tolerate the procedure, the ambience of the clinic room, the uniformity of bolus trials and conductivity, responsibilities of team members, and the importance of adequate procedural preparation. Looking to the future, the insights from this thesis aim to illustrate the potential clinical value of quantifying swallowing biomechanics by advanced, integrated manometry impedance technology. With the characterisation of swallowing pathophysiology according to quantitative and reliable contractility, distension and bolus flow timing measurements this may lead to enhanced specificity of patient management

and potentially, the development of innovative therapies and interventions based on revealed swallowing biomechanics in larger cohorts.

10.7 Future Directions

This thesis contributes relevant information towards the characterisation of paediatric OPD and highlights the need to further investigate these methods so that the clinical value of P-HRM-I may continue to be revealed.

10.7.1 Correlation with Other Instrumental Assessments

An important and imminent future direction for P-HRM-I research is the correlation with traditional, instrumental technologies such as VFSS, as has been achieved with adults (189, 190, 193, 236, 237, 247), and in a single paediatric study (184). Given the visuo-perceptual value of VFSS in characterising kinematics of swallowing physiology, airway protective mechanisms, and the evidence of airway invasion, if correlated with pressure flow parameters in larger than previously studied cohorts, such research will significantly advance the field of paediatric dysphagia assessment, and potentially the ongoing management of children with OPD. Additionally, with the recent ability to derive quantitative VFSS swallowing parameters and airway kinematics with semi-automated analysis (81, 96, 98, 100, 101), future correlations with pressure flow parameters will be easier to apply and more reliable. We see particular value in the future exploration of radiological timing measures and those generated from P-HRM-I i.e. BPT, DCL and UOS RT. This would allow the intricately coordinated events of the swallowing mechanism to be investigated further and in more detail, if interpreted in relation to the other metrics defining pharyngeal and UOS contractility and distensibility. The exploration of such swallowing biomechanical profiles in larger paediatric cohorts stratified by age group and medical condition would allow for a more comprehensive investigation of swallowing pathophysiology and the underlying biomechanics related to OPD features such as aspiration, residue, and the relating clinical symptoms, e.g., coughing, wet breath sounds, and nasal regurgitation. Recognising that no single test delivers complete assessment of the functions that ensure safe and effective swallowing, comparing the parameters generated by VFSS and

P-HRM-I methodologies may further validate and inform the diagnostic value that each methodology offers the clinician.

10.7.2 Therapeutic Outcomes

The P-HRM-I pressure flow parameters explored in this research program may also be applied as objective swallowing biomechanical outcome measures for therapeutic trials, such as pre- and post- laryngeal cleft repair (349), unilateral vocal fold paralysis repair (350), UOS achalasia repair (336, 337) post supraglottoplasty in severe cases of laryngomalacia (351), and post TOF repair known to impact pharyngeal swallowing in some cases (352). Pharyngeal outcomes could also be explored in other oesophageal conditions such as congenital vascular rings (353). If applied in the appropriate patient, of adequate age and cognitive skills, swallowing manoeuvres and strategies may also be tested to characterise the impact of swallowing therapies such as the widely implemented chin tuck and effortful swallowing strategies on paediatric biomechanics. As bolus modifications are widely implemented therapeutically in children with OPD, the intricate physiological characteristics of paediatric swallowing modulation should be investigated. The unique biomechanical features associated with challenging the paediatric swallowing mechanism need to be investigated to clarify the impact of bolus size and consistency in relation to a child's age and medical condition. Additionally, swallowing behaviours during self-moderated drinking, single bolus administration and sequential swallowing could also be established according to a range of paediatric drinking equipment (e.g., teat/valve flow and size, straw size, and open cup). Without the constraints of radiology there is scope for HRM to define the pharyngeal and UOS breast-feeding mechanics in babies, however, the conductive properties of breastmilk will need to be determined before impedance measurements are integrated.

10.7.3 Guiding Clinical Decision Making

The swallowing mechanism changes dynamically in relation to growth and development throughout childhood, and in cases of paediatric degenerative conditions. Quantitative

parameters may be beneficial to measure the deterioration of swallow biomechanics. The added diagnostic information from P-HRM-I in relation to pathophysiology may be particularly useful in guiding clinical decisions for implementation of alternative feeding methods. Recognising the impact of tube feeding on quality of life (354) and the importance of pulmonary health in palliative care, these methods may assist in decisions around safety of oral food/liquid experiences in a child's feeding regime.

If pressure flow measurements are to benefit the clinical decisions of paediatric OPD management in the future, further exploration in much larger and more homogeneous cohorts is required. This would allow for patient stratification according to age group, medical condition and severity of OPD symptoms. Describing the swallowing biomechanics at different stages of childhood and recognised clinical severity levels (using quantified measures such as DMSS and FOIS) would provide age-specific reference ranges of swallowing pathophysiology according to OPD severity level and medical condition. Formal translation of swallowing parameters across instrumentations is also required and may lead towards multi-modal skill sets for clinicians, and in turn more comprehensive diagnosis of the swallowing mechanism overall, in patients with OPD. This may enhance expertise for the selection and interpretation of evaluation methods, ultimately optimising outcomes, and quality of life in patients with OPD.

10.7.4 Tracking Changes over Time

Future studies could investigate the prognostic value of P-HRM-I pressure flow parameters if children with OPD are tracked over time in relation to: i) the degree of swallowing pathophysiology defined by quantitative pressure flow parameters; ii) the presence of associated health factors known to influence OPD severity, such as structural abnormalities (e.g. presence and degree of airway malacia; laryngeal cleft), and neurological/developmental health, including the impact on a child's ability to exert their breath rate in relation to gross motor mobility skills (355); and iii) the functional oral intake status (311) and the precipitating adverse health outcomes that may have occurred for a child during the tracking period.

Intentions for such a study are twofold: first to define age-specific reference ranges within the pressure flow parameters according to OPD severity; and second to ascertain the requirement and efficacy of particular OPD management strategies in relation to swallowing pathophysiology, highlighting particular combinations of factors which help or hinder the overall health outcomes of children with OPD.

10.8 Thesis Conclusion

This thesis demonstrates that P-HRM-I techniques provide important information towards the assessment of swallowing biomechanics. A clear influence of catheter diameter on pharyngeal pressure flow parameters has been shown; hence, we recommend all manometric results are interpreted in relation to catheter specifications. Pressure flow parameters can detect distinct features of swallowing neuromodulation to altered bolus volumes and viscosity levels. A new consideration for P-HRM-I analysis is the impact of piecemeal deglutition, and this work has outlined an approach using admittance curves to guide selection of swallows from topographical piecemeal sequences. Exploring paediatric OPD and the application of P-HRM-I in children, we demonstrated that UOS dysfunction was significantly associated with symptoms of OPD. This highlights the potential contribution of, and necessary assessment of UOS biomechanics when evaluating OPD in paediatric patients. Our research suggests a more comprehensive understanding of paediatric swallowing pathophysiology will be developed if P-HRM-I metrics are generated from standardised protocols, in larger cohorts stratified by age and medical condition. Additionally, we have shown repeat P-HRM-I testing is obtainable and studies can be optimised if patient age and suitability is determined. With provision of quantitative swallowing measurements, the future application of P-HRM-I in the paediatric setting may be particularly beneficial as an outcome measure of therapeutic interventions. The clinical value of P-HRM-I techniques is promising and will continue to be substantiated by ongoing investigation in future patient cohorts.

Bibliography

1. Newman LA, Keckley C, Petersen MC, Hamner A. Swallowing function and medical diagnoses in infants suspected of dysphagia. Pediatrics. 2001;108(6):e106-e.

2. Field D, Garland M, Williams K. Correlates of specific childhood feeding problems. J Paediatr Child Health. 2003;39(4):299-304.

3. Lefton-Greif MA, Arvedson JC. Pediatric feeding/swallowing: yesterday, today, and tomorrow. Sem Speech Lang. 2016;1(212):298-309.

4. Rommel N, De Meyer A-M, Feenstra L, Veereman-Wauters G. The complexity of feeding problems in 700 infants and young children presenting to a tertiary care institution. J Pediatr Gastroenterol Nutr. 2003;37(1):75-84.

5. Goday PS, Huh SY, Silverman A, Lukens CT, Dodrill P, Cohen SS, et al. Pediatric feeding disorder: consensus definition and conceptual framework. J Pediatr Gastroenterol Nutr. 2019;68(1):124-9.

6. Arvedson J, Brodsky L, Lefton-Greif MA. Pediatric swallowing and feeding: assessment and management. 3rd ed: Plural Publishing; 2020 2020.

7. Wolf LS, Glass RP, Carr AB. Feeding and swallowing disorders in infancy: assessment and management. Tucson, Arizona: Therapy Skill Builders; 1992.

8. Dodrill P, Gosa MM. Pediatric dysphagia: physiology, assessment, and management. Ann Nutr Metab. 2015;66(5):24-31.

9. Serel SA, Demir N, Karaduman AA. Both pharyngeal and esophageal phases of swallowing are associated with recurrent pneumonia in pediatric patients. Clin Respir J. 2018;12(2):767-71.

10. Borders JC, Brates D. Use of the penetration-aspiration scale in dysphagia research: a systematic review. Dysphagia. 2020;35(4):583-97.

11. Arvedson J. Assessment of pediatric dysphagia and feeding disorders: clinical and instrumental approaches. Dev Disabil Res Rev. 2008;14(2):118-27.

12. Miller CK. Aspiration and swallowing dysfunction in pediatric patients. ICAN: Infant Child Adolesc Nutr. 2011;3(6):336-43.

13. Miller CK, Maybee J, Prager J, Pentiuk S. Kendig and Chernick's disorders of the respiratory tract in children. In: Wilmott RW, Deterding R, Li A, Ratjen F, Sly P, Zar H, et al., editors. Feeding and swallowing disorders. 9th ed. Philadelphia: Elsevier Inc.; 2019. p. 1106-13.e1.

14. Prasse JE, Kikano GE. An overview of pediatric dysphagia. Clin Pediatr. 2009;48(3):247-51.

15. Mercado-Deane MG, Burton EM, Harlow SA, Glover AS, Deane DA, Guill MF, et al. Swallowing dysfunction in infants less than 1 year of age. Pediatr Radiol. 2001;31(6):423-8.

16. Tutor JD, Gosa MM. Dysphagia and aspiration in children. Pediatr Pulmonol. 2012;47(4):321-37.

17. Costa MMB. Videofluoroscopy: the gold standard exam for studying swallowing and its dysfunction. Arq Gastroenterol. 2010;47(4):327-8.

18. Belafsky PC, Kuhn MA. The videofluoroscopic swallow study technique and protocol. Springer New York; 2014. p. 7-13.

19. Lawlor CM, Choi S. Diagnosis and management of pediatric dysphagia. JAMA Otolaryngol Head Neck Surg. 2020;146(2):183.

20. Geddes DT, Sakalidis VS. Ultrasound imaging of breastfeeding--A window to the inside: methodology, normal appearances, and application. J Hum Lact. 2016;32(2):340-9.

21. Ferris L, Omari T. Pharyngeal manometry in pediatric dysphagia assessment. Perspect ASHA Spec Interest Groups. 2019;4(4):656-82.

22. Borowitz KC, Borowitz SM. Feeding problems in infants and children: assessment and etiology. Pediatr Clin North Am. 2018;65(1):59-72.

23. Kerzner B, Milano K, MacLean WC, Berall G, Stuart S, Chatoor I. A practical approach to classifying and managing feeding difficulties. Pediatr. 2015;135(2):344-53.

24. 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.

25. Logemann JA. Evaluation and treatment of swallowing disorders. Second Edi ed. Austin Texas: Pro-Ed; 1998.

26. Rudolph CD, Thompson Link D. Feeding disorders in infants and children. Pediatr Clin North Am. 2002;49(1):97-112.

27. Arvedson JC, Brodsky L. Pediatric swallowing and feeding: assessment and management. 2nd ed. Albany, NY.: Singular Publishing Group; 2002.

28. Chumpitazi B, Nurko S. Pediatric gastrointestinal motility disorders: challenges and a clinical update. Gastroenterol Hepatol. 2008;4(2):140-8.

29. Lefton-Greif MA, Okelo SO, Wright JM, Collaco JM, McGrath-Morrow SA, Eakin MN. Impact of children's feeding/swallowing problems: validation of a new caregiver instrument. Dysphagia. 2014;29(6):671-7.

30. Arvedson JC, Lefton-Greif MA. Instrumental assessment of pediatric dysphagia. Sem Speech Lang. 2017;38(2):135-46.

31. Arvedson J, Clark H, Lazarus C, Schooling T, Frymark T. Evidence-based systematic review: effects of oral motor interventions on feeding and swallowing in preterm infants. Am J Speech Lang Pathol. 2010;19(4):321-40.

32. Chun R, Sitton M, Tipnis N, Arvedson JC, Rao A, Dranove J, et al. Endoscopic cricopharyngeal myotomy for management of cricopharyngeal achalasia (CA) in an 18-month-old child. Laryngoscope. 2013;123(3):797-800.

33. Fucile S, Gisel EG, McFarland DH, Lau C. Oral and non-oral sensorimotor interventions enhance oral feeding performance in preterm infants. Dev Med Child Neurol. 2011;53(9):829-35.

34. Gisel E. Interventions and outcomes for children with dysphagia. Dev Disabil Res Rev. 2008;14(2):165-73.

35. Weir KA, McMahon S, Taylor S, Chang AB. Oropharyngeal aspiration and silent aspiration in children. Chest. 2011;140(3):589-97.

36. Hiorns MP, Ryan MM. Current practice in paediatric videofluoroscopy. Pediatr Radiol. 2006;36(9):911-9.

37. Jaffer NM, Ng E, Wing-Fai Au F, Steele CM. Fluoroscopic evaluation of oro-pharyngeal dysphagia: anatomy, technique and common etiologies. Am J Roentgenol. 2015;204(1):49-58.

38. Martin-Harris B, Jones B. The videofluorographic swallowing study. Phys Med Rehabil Clin North Am. 2008;19(4):769-85.

39. Borr C, Hielscher-Fastabend M, Lücking A. Reliability and validity of cervical auscultation. Dysphagia. 2007;22(3):225-34.

40. Frakking TT, Chang AB, O'Grady KAF, David M, Weir KA. Reliability for detecting oropharyngeal aspiration in children using cervical auscultation. Int J Speech Lang Pathol. 2017;19(6):569-77.

41. McAllister S, Kruger S, Doeltgen S, Tyler-Boltrek E. Implications of variability in clinical bedside swallowing asessment practices by speech-language pathologists. Dysphagia. 2016;31(5):650-62.

42. Reynolds EW, Vice FL, Gewolb IH. Variability of swallow-associated sounds in adults and infants. Dysphagia. 2009;24(1):13-9.

43. Romano M, Schultz T, Tai A, White S. The diagnostic test accuracy of clinical swallow assessment for oropharyngeal aspiration: a systematic review. JBI Database of Systematic Rev Implement Rep. 2014;12(8):259-329.

44. Calvo I, Conway A, Henriques F, Walshe M. Diagnostic accuracy of the clinical feeding evaluation in detecting aspiration in children: a systematic review. Dev Med Child Neurol. 2016;58(6):541-53.

45. Soyer T, Yalcin S, Arslan SS, Demir N, Tanyel FC. Pediatric Eating Assessment Tool-10 as an indicator to predict aspiration in children with esophageal atresia. J Pediatr Surg. 2017;52(10):1576-9.

46. Sheppard JJ, Hochman R, Baer C. The dysphagia disorder survey: validation of an assessment for swallowing and feeding function in developmental disability. Res Dev Disabil. 2014;35(5):929-42.

47. Crary MA, Mann GDC, 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.

48. Duncan DR, Mitchell PD, Larson K, Rosen RL. Presenting signs and symptoms do not predict aspiration risk in children. J Pediatr. 2018;201:141-6.

49. Doeltgen SH, McAllister S, Murray J, Ward EC, Pretz JE. Reasoning and decision making in clinical swallowing examination. Curr Phys Med Rehabil Rep. 2018;6(3):171-7.

50. Benfer KA, Weir KA, Boyd RN. Clinimetrics of measures of oropharyngeal dysphagia for preschool children with cerebral palsy and neurodevelopmental disabilities: a systematic review. Dev Med Child Neurol. 2012;54(9):784-95.

51. Heckathorn D-EE, Speyer R, Taylor J, Cordier R. Systematic review: non-instrumental swallowing and feeding assessments in pediatrics. Dysphagia. 2016;31(1):1-23.

52. Coppens CH, van den Engel-Hoek L, Scharbatke H, de Groot SAF, Draaisma JMT. Dysphagia in children with repaired oesophageal atresia. Eur J Pediatr. 2016;175(9):1209-17.

53. Yi YG, Shin H-i. Psychometrics of the Functional Oral Intake Scale for infants. Front Pediatr. 2019;7(April):156.

54. Christiaanse ME, Mabe B, Russell G, Simeone TL, Fortunato J, Rubin B. Neuromuscular electrical stimulation is no more effective than usual care for the treatment of primary dysphagia in children. Pediatr Pulmonol. 2011;46(6):559-65.

55. Ferris L, Rommel N, Doeltgen S, Scholten I, Kritas S, Abu-Assi R, et al. Pressure flow analysis for the assessment of pediatric oropharyngeal dysphagia. J Pediatr. 2016;177:279-85.

56. Kotsimbos T, Armstrong D, Buckmaster N, de Looze F, Hart D, Holmes P, et al. Respiratory infectious disease burden in Australia: initiative of The Australian Lung Foundation. 2007.

57. Zhang S, Sammon PM, King I, Andrade L, Toscano CM, Araujo SN, et al. Cost of management of severe pneumonia in young children: systematic analysis. J Global Health. 2016;6(1).

58. East L, Nettles K, Vansant A, Daniels SK. Evaluation of oropharyngeal dysphagia with the videofluoroscopic swallowing study. J Radiol Nurs. 2014;33(1):9-13.

59. 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. 2018;34(1):2-33.

60. Cock C, Omari T. Diagnosis of swallowing disorders: how we interpret pharyngeal manometry. Curr Gastroenterol Rep. 2017;19(3):11.

61. Giraldo-Cadavid LF, Leal-Leaño 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.

62. Lee JW, Randall DR, Evangelista LM, Kuhn MA, Belafsky PC. Subjective assessment of videofluoroscopic swallow studies. Otolaryngol Head Neck Surg. 2017;156(5):019459981769127-.

63. Lefton-Greif MA, McGrattan KE, Carson KA, Pinto JM, Wright JM, Martin-Harris B. First steps towards development of an instrument for the reproducible quantification of oropharyngeal swallow physiology in bottle-fed children. Dysphagia. 2018;33(1):76-82.

64. Newman LA, Cleveland R, Blickman J, Robert H, Jaramillo D. Videofluoroscopic analysis of the infant swallow. Invest Radiol. 1991;26(10):870-73.

65. Lo Re G, Vernuccio F, Di Vittorio ML, Scopelliti L, Di Piazza A, Terranova MC, et al. Swallowing evaluation with videofluoroscopy in the paediatric population. Acta Otorhinolaryngol Ital. 2019;39(5):279-88.

66. Steele CM, Grace-Martin K. Reflections on clinical and statistical use of the penetration-aspiration scale. Dysphagia. 2017;32(5):601-16.

67. Weckmueller J, Easterling C, Arvedson J. Preliminary temporal measurement analysis of normal oropharyngeal swallowing in infants and young children. Dysphagia. 2011;26(2):135-43.

68. Weir KA. Oropharyngeal aspiration and oropharyngeal dysphagia in children: assessment, treatment and relationship with respiratory disease [Dissertation]. Brisbane, Qld.: University of Queensland; 2014.

69. Rosenbek JC, Robbins JA, Roecker EB, Coyle JL, Wood JL. A penetration-aspiration scale. Dysphagia. 1996;11(2):93-8.

70. DeMatteo C, Matovich D, Hjartarson A. Comparison of clinical and videofluoroscopic evaluation of children with feeding and swallowing difficulties. Dev Med Child Neurol. 2005;47(3):149-57.

71. 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.

72. Mérey C, Kushki A, Sejdi E, Berall G, Chau T. Quantitative classification of pediatric swallowing through accelerometry. J Neuro Eng Rehabil. 2012;9(1):1-8.

73. Kuhlemeier KV, Yates P, Palmer JB. Intra- and interrater variation in the evaluation of videofluorographic swallowing studies. Dysphagia. 1998;13(3):142-7.

74. McCullough GH, Wertz RT, Rosenbek JC, Mills RH, Webb WG, Ross KB. Inter- and intrajudge reliability for videofluoroscopic swallowing evaluation measures. Dysphagia. 2001;16(2):110-8.

75. Stoeckli SJ, Huisman TAGM, Seifert BAGM, Martin-Harris BJW. Interrater reliability of videofluoroscopic swallow evaluation. Dysphagia. 2003;18(1):53-7.

76. 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.

77. Patel T, Clemmens C, Bradburn K, Beckstrand M, McGhee H, McKelvey K, et al. Effect of a standardized fluoroscopic procedural approach on fluoroscopy time during infant modified barium swallow studies. Int J Pediatr Otorhinolaryngol. 2020;138:110396.

78. Weir KA, McMahon SM, Long G, Bunch JA, Pandeya N, Coakley KS, et al. Radiation doses to children during modified barium swallow studies. Pediatr Radiol. 2007;37(3):283-90.

79. 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.

80. Cockerill H, van den Engel-Hoek L, Harding C. Assessing children's swallowing: parent and professional perceptions. Tizard Learn Disabil Rev. 2016;21(3):117-25.

81. Baijens L, Barikroo A, Pilz W. Intrarater and interrater reliability for measurements in videofluoroscopy of swallowing. Eur J Radiol. 2013;82(10):1683-95.

82. Henderson M, Miles A, Holgate V, Peryman S, Allen J. Application and verification of quantitative objective videofluoroscopic swallowing measures in a pediatric population with dysphagia. J Pediatr. 2016;178:200-5.e1.

83. Leonard RJ, Kendall KA, McKenzie S, Gonçalves MI, Walker A. Structural displacements in normal swallowing: a videofluoroscopic study. Dysphagia. 2000;15(3):146-52.

84. Andreoli SM, Wilson BL, Swanson C. Neuromuscular electrical stimulation improves feeding and aspiration status in medically complex children undergoing feeding therapy. Int J Pediatr Otorhinolaryngol. 2019;127:109646.

85. Irace AL, Dombrowski ND, Kawai K, Dodrill P, Perez J, Hernandez K, et al. Aspiration in children with unilateral vocal fold paralysis. Laryngoscope. 2019;129(3):569-73.

86. Irace AL, Dombrowski ND, Kawai K, Watters K, Choi S, Perez J, et al. Evaluation of aspiration in infants with laryngomalacia and recurrent respiratory and feeding difficulties. JAMA Otolaryngol Head Neck Surg. 2019;146-51(2):146.

87. Stewart AJ, Butler CR, Muthialu N, Sell D, Marchant J, Hewitt RJD, et al. Swallowing outcomes in children after slide tracheoplasty. Int J Pediatr Otorhinolaryngol. 2018;108:85-90.

88. 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.

89. Donohue C, Khalifa Y, Perera S, Sejdić E, Coyle JL. How closely do machine ratings of duration of UES opening during videofluoroscopy approximate clinician ratings using temporal kinematic analyses and the MBSImP? Dysphagia. 2020;21:1-2.

90. Jordan Hazelwood R, 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.

91. Martin-Harris B, Carson KA, Pinto JM, Lefton-Greif MA. BaByVFSSImP©) A novel measurement tool for videofluoroscopic assessment of swallowing impairment in bottle-fed babies: establishing a standard. Dysphagia. 2020;35(1):90-8.

92. Beall J, Hill EG, Armeson K, Garand KLF, Davidson KH, Martin-Harris B. Classification of physiologic swallowing impairment severity: a latent class analysis of modified barium swallow impairment profile scores. Am J Speech Lang Pathol. 2020;29(2S):1001-11.

93. Molfenter SM, Steele CM. Kinematic and temporal factors associated with penetration–aspiration in swallowing liquids. Dysphagia. 2014;29(2):269-76.

94. Aung MSH, Goulermas JY, Stanschus S, Hamdy S, Power M. Automated anatomical demarcation using an active shape model for videofluoroscopic analysis in swallowing. Med Eng Phys. 2010;32(10):1170-9.

95. Noorwali S. Semi-automatic tracking of the hyoid bone and the epiglottis movements in digital videofluoroscopic images. London, Ontario, Canada: The University of Western Ontario; 2013.

96. Kellen PM, Becker DL, Reinhardt JM, Van Daele DJ. Computer-assisted assessment of hyoid bone motion from videofluoroscopic swallow studies. Dysphagia. 2010;25(4):298-306.

97. Mancopes R, Peladeau-Pigeon M, Barrett E, Guran A, Smaoui S, Pasqualoto AS, et al. Quantitative videofluoroscopic analysis of swallowing physiology and function in individuals with chronic obstructive pulmonary disease. J Speech Lang Hear Res. 2020;63(11):3643-58.

98. 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.

99. Cabib C, Nascimento W, Rofes L, Arreola V, Tomsen N, Mundet L, et al. Neurophysiological and biomechanical evaluation of the mechanisms which impair safety of swallow in chronic post-stroke patients. Translational Stroke Research. 2020;11(1):16-28.

100. Leonard R, Kendall K. Dynamic swallow study: objective measures and normative data in adults. In: Leonard RJ, Kendall KA, editors. Dysphagia assessment and treatment planning - A team approach. 4th ed. San Diego, CA 92123: Plural Publishing; 2019.

101. Dharmarathna I, Miles A, Allen JE. Predicting penetration-aspiration through quantitative swallow measures of children: a videofluoroscopic study. Eur Arch Otorhinolaryngol. 2021:1-10.

102. Dharmarathna I, Miles A, Fuller L, Allen J. Quantitative video-fluoroscopic analysis of swallowing in infants. Int J Pediatr Otorhinolaryngol. 2020;138:110315.

103. Hersh C, Wentland C, Sally S, de Stadler M, Hardy S, Fracchia MS, et al. Radiation exposure from videofluoroscopic swallow studies in children with a type 1 laryngeal cleft and pharyngeal dysphagia: a retrospective review. International Journal of Pediatric Otorhinolaryngology. 2016;89(Oct):92-6.

104. Langmore S, Schatz K, Olsen N. Fiberoptic endoscopic examination of swallowing safety: a new procedure. Dysphagia. 1988;2(4):216-9.

105. Hiss S, Postma G. Fiberoptic endoscopic evaluation of swallowing. Laryngoscope. 2003;113(8):1386-93.

106. Miller CK, Willging JP. Fiberoptic endoscopic evaluation of swallowing in infants and children: protocol, safety, and clinical efficacy: 25 years of experience. Annals of Otology, Rhinology and Laryngology. 2020;129(5):469-81.

107. Willging P. Endoscopic evaluation of swallowing in children. International Journal of Pediatric Otorhinolaryngology. 1995;32:S107-8.

108. Hartnick CJ, Hartley BEJ, Miller C, Willging JP. Pediatric fiberoptic endoscopic evaluation of swallowing. Annals of Otology, Rhinology and Laryngology. 2000;109(11):996-9.

109. Vetter-Laracy S, Osona B, Roca A, Peña-Zarza JA, Gil JA, Figuerola J. Neonatal swallowing assessment using fiberoptic endoscopic evaluation of swallowing (FEES). Pediatric Pulmonology. 2018;53(4):437-42.

110. Willette S, Molinaro LH, Thompson DM, Schroeder JW. Fiberoptic examination of swallowing in the breastfeeding infant. Laryngoscope. 2015;126(7):1681-6.

111. Thompson DM. Laryngopharyngeal sensory testing and assessment of airway protection in pediatric patients. American Journal of Medicine. 2003;115(3):166-8.

112. Sitton M, Arvedson J, Visotcky A, Braun N, Kerschner J, Tarima S, et al. Fiberoptic endoscopic evaluation of swallowing in children: feeding outcomes related to diagnostic groups and endoscopic findings. International Journal of Pediatric Otorhinolaryngology. 2011;75(8):1024-31.

113. Dziewas R, Auf dem Brinke M, Birkmann U, Brauer G, Busch K, Cerra F, et al. Safety and clinical impact of FEES - results of the FEES-registry. Neurol Res Pract. 2019;1:16.

114. Farneti D, Genovese E. Endoscopic criteria in assessing severity of swallowing disorders. InTech; 2015.

115. Dharmarathna I, Miles A, Allen J. Twenty years of quantitative instrumental measures of swallowing in children: a systematic review. European Journal of Pediatrics. 2020;179(2):203-23.

116. Da Silva AP, Lubianca Neto JF, Santoro PP. Comparison between videofluoroscopy and endoscopic evaluation of swallowing for the diagnosis of dysphagia in children. Otolaryngology - Head and Neck Surgery. 2010;143(2):204-9.

117. Leder SB, Karas DE. Fiberoptic endoscopic evaluation of swallowing in the pediatric population. Laryngoscope. 2000;110(7):1132-6.

118. Coltrera MD. Ultrasound physics in a nutshell. Otolaryngologic Clinics of North America. 2010;43(6):1149-59, v.

119. Arens C, Weigt J, Schumacher J, Kraft M. Ultrasound of the larynx, hypopharynx and upper oesophagus. HNO. 2011;59(2):145-54.

120. Kacar S. Transcutaneous cervical esophagus ultrasound in adults: relation with ambulatory 24-h pH-monitoring and esophageal manometry. World Journal of Gastroenterology. 2007;13(39):5245.

121. Mittal RK, Liu J, Puckett JL, Bhalla V, Bhargava V, Tipnis N, et al. Sensory and motor function of the esophagus: lessons from ultrasound imaging. Gastroenterology. 2005;128(2):487-97.

122. Wilcox A, Jackson D, Jones J, Thomas S. Bolus detection in the proximal esophagus using pulse-echo ultrasound: a feasibility study. Otolaryngology - Head and Neck Surgery. 2020;163(3):569-71.

123. Mittal RK, Bhalla V. Oesophageal motor functions and its disorders. Gut. 2004;53(10):1536-42.

124. Dall'Asta A, Grisolia G, Nanni M, Volpe N, Schera GBL, Frusca T, et al. Sonographic demonstration of fetal esophagus using three-dimensional ultrasound imaging. Ultrasound in Obstetrics & Gynecology. 2019;54(6):746-51.

125. McClellan H, Kent J, Hepworth A, Hartmann P, Geddes D. Persistent nipple pain in breastfeeding mothers associated with abnormal infant tongue movement. International Journal of Environmental Research and Public Health. 2015;12(9):10833-45.

126. Geddes DT, Chadwick LM, Kent JC, Garbin CP, Hartmann PE. Ultrasound imaging of infant swallowing during breast-feeding. Dysphagia. 2010;25(3):183-91.

127. Sakalidis VS, Williams TM, Garbin CP, Hepworth AR, Hartmann PE, Paech MJ, et al. Ultrasound imaging of infant sucking dynamics during the establishment of lactation. Journal of Human Lactation. 2013;29(2):205-13.

128. Mizuno A, Ueda A. Development of sucking behavior in infants with Down's syndrome. Acta Paediatrica. 2001;12(90):1384-8.

129. Miller JL, Kang SM. Preliminary ultrasound observation of lingual movement patterns during nutritive versus non-nutritive sucking in a premature infant. Dysphagia. 2007;22(2):150-60.

130. Jadcherla SR, Gupta A, Wang M, Coley BD, Fernandez S, Shaker R. Definition and implications of novel pharyngo-glottal reflex in human infants using concurrent manometry ultrasonography. American Journal of Gastroenterology. 2009;104(10):2572-82.

131. Kuhl V, Eicke BM, Dieterich M, Urban PP. Sonographic analysis of laryngeal elevation during swallowing. Journal of Neurology. 2003;250(3):333-7.

132. Scarborough DR, Waizenhofer S, Siekemeyer L, Hughes M. Sonographically measured hyoid bone displacement during swallow in preschool children: a preliminary study. Journal of Clinical Ultrasound. 2010;38(8):430-4.

133. Abdelrahman AS, Abdeldayem EH, Bassiouny S, Elshoura HM. Role of ultrasound in evaluation of pharyngeal dysphagia in children with cerebral palsy. Egyptian Journal of Radiology and Nuclear Medicine. 2019;50(1).

134. Riley A, Miles A, Steele CM. An exploratory study of hyoid visibility, position, and swallowing-related displacement in a pediatric population. Dysphagia. 2019;34(2):248-56.

135. Stone M. A guide to analysing tongue motion from ultrasound images. Clinical Linguistics & Phonetics. 2005;19(6-7):455-501.

136. Dodds WJ, Hogan WJ, Lydon SB, Stewart ET, Stef JJ, Arndorfer RC. Quantitation of pharyngeal motor function in normal human subjects. Journal of Applied Physiology. 1975;39(4):692-6.

137. Castell JA, Dalton CB, Castell D. Pharyngeal manometry and upper esophageal sphincter in humans. American Journal of Physiology - Gastrointestinal and Liver Physiology. 1990;258(2):G173-8.

138. Dent J. A new technique for continuous sphincter pressure measurement. Gastroenterology. 1976;71(2):263-7.

139. Kahrilas PJ, Dent J, Dodds WJ, Hogan WJ, Arndorfer RC. A method for continuous monitoring of upper esophageal sphincter pressure. Digestive Diseases and Sciences. 1987;32(2):121-8.

140. Rohof WOA, Bredenoord AJ. Chicago classification of esophageal motility disorders: lessons learned. Current Gastroenterology Reports. 2017;19(8):1-6.

141. Nativ-Zeltzer N, Kahrilas PJ, Logemann JA. Manofluorography in the evaluation of oropharyngeal dysphagia. Dysphagia. 2012;27(2):151-61.

142. Carlson DA, Kahrilas PJ. How to effectively use high-resolution esophageal manometry. Gastroenterology. 2016;151(5):789-92.

143. Pandolfino JE. High-resolution manometry: is it better for detecting esophageal disease? Gastroenterology & Hepatology. 2010;6(10):632-4.

144. Patel A, Mirza DF, Gyawali CP. Optimizing the high-resolution manometry (HRM) study protocol. Neurogastroenterology & Motility. 2015;27(2):300-4.

145. Rommel N, van Wijk M, Boets B, Hebbard G, Haslam R, Davidson G, et al. Development of pharyngo-esophageal physiology during swallowing in the preterm infant. Neurogastroenterology & Motility. 2011;23(10):e401-8.

146. Ghosh SK, Pandolfino JE, Zhang Q, Jarosz A, Kahrilas PJ. Deglutitive upper esophageal sphincter relaxation: a study of 75 volunteer subjects using solid-state high-resolution manometry. American Journal of Physiology - Gastrointestinal and Liver Physiology. 2006;291(3):G525-31.

147. 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. American Journal of Physiology - Gastrointestinal and Liver Physiology. 2016;311(1):G84-90.

148. O'Rourke A, Humphries K, Lazar A, Martin-Harris B. The pharyngeal contractile integral is a useful indicator of pharyngeal swallowing impairment. Neurogastroenterology & Motility. 2017;29(12):1-7.

149. Roman S, Kahrilas PJ, Boris L, Bidari K, Luger D, Pandolfino JE. High-resolution manometry studies are frequently imperfect but usually still interpretable. Clinical Gastroenterology and Hepatology. 2011;9(12):1050-5.

150. Ryu JS, Park D, Kang JY. Application and interpretation of high-resolution manometry for pharyngeal dysphagia. Journal of Neurogastroenterology and Motility. 2015;21(2):283-7.

151. 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.

152. McCulloch TM, Hoffman MR, Ciucci MR. High-resolution manometry of pharyngeal swallow pressure events associated with head turn and chin tuck. Annals of Otology, Rhinology and Laryngology. 2010;119(6):369-76.

153. 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.

154. 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. American Journal of Gastroenterology. 2011;106(10):1796-802.

155. 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.

156. Jones C. Pharyngeal bolus propulsion: relationships between pharyngeal pressures, contraction, and residue. 10th ESSD Congress, Dysphagia Management across Lifespan; 8-10 October 2020; Online Virtual Congress2020.

157. Jones CA, Meisner EL, Broadfoot CK, Rosen SP, Samuelsen CR, McCulloch TM. Methods for measuring swallowing pressure variability using high-resolution manometry. Frontiers in Applied Mathematics and Statistics. 2018;4(July):1-17.

158. Clouse RE, Staiano A, Alrakawi A, Haroian L. Application of topographical methods to clinical esophageal manometry. American Journal of Gastroenterology. 2000;95(10):2720-30.

159. 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.

160. Rosen SP, Jones CA, McCulloch TM. Pharyngeal swallowing pressures in the base-of-tongue and hypopharynx regions identified with three-dimensional manometry. Laryngoscope. 2016;127(9):1989-95.

161. Chitose Si, Shin Y, Sato K, Hamakawa S, Fukahori M, Ono T, et al. Three-dimensional imaging of upper esophageal sphincter resting pressure. Laryngoscope Investigative Otolaryngology. 2019;4(6):645-52.

162. Guiu Hernandez E, Gozdzikowska K, Jones R, Huckabee M-L. Comparison of unidirectional and circumferential manometric measures within the pharyngoesophageal segment: an exploratory study. European Archives of Oto-Rhino-Laryngology. 2018;275(9):2303-10.

163. Kern MK, Balasubramanian G, Sanvanson P, Agrawal D, Wuerl A, Shaker R. Pharyngeal peristaltic pressure variability, operational range, and functional reserve. American Journal of Physiology - Gastrointestinal and Liver Physiology. 2017;312(5):G516-G25.

164. 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. International Journal of Otolaryngology. 2016;2016.

165. Dejaeger E, Pelemans W, Bibau G, Ponette E. Manofluorographic analysis of swallowing in the elderly. Dysphagia. 1994;9(3):156-61.

166. McConnel FMS, Cerenko D, Hersh T, Weil LJ. Evaluation of pharyngeal dysphagia with manofluorography. Dysphagia. 1988;2(4):187-95.

167. McConnel FMS, Hester TR, Mendelsohn MS, Logemann JA. Manofluorography of deglutition after total laryngopharyngectomy. Plastic and Reconstructive Surgery. 1988;81(3):346-51.

168. 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. Neurogastroenterology & Motility. 2016;28(5):721-31.

169. Ozgursoy OB, Salassa JR. Manofluorographic and functional outcomes after endoscopic laser cricopharyngeal myotomy for cricopharyngeal bar. Otolaryngology - Head and Neck Surgery. 2010;142(5):735-40.

170. Rommel N, Dejaeger E, Bellon E, Smet M, Veereman-Wauters G. Videomanometry reveals clinically relevant parameters of swallowing in children. International Journal of Pediatric Otorhinolaryngology. 2006;70(8):1397-405.

171. Salassa JR, DeVault KR, McConnel FMS. Proposed catheter standards for pharyngeal manofluorography (videomanometry). Dysphagia. 1998;13(2):105-10.

172. Ueha R, Goto T, Sato T, Nativ-Zeltzer N, Shen SC, Nito T, et al. High resolution manofluorographic study in patients with multiple system atrophy: possible early detection of upper esophageal sphincter and proximal esophageal abnormality. Frontiers in Medicine. 2018;5:Art. 286.

173. Pal A, Williams RB, Cook IJ, Brasseur JG. Intrabolus pressure gradient identifies pathological constriction in the upper esophageal sphincter during flow. American Journal of Physiology - Gastrointestinal and Liver Physiology. 2003;285(5):G1037-G48.

174. Williams RBH, Wallace KL, Ali GN, Cook IJ. Biomechanics of failed deglutitive upper esophageal sphincter relaxation in neurogenic dysphagia. American Journal of Physiology - Gastrointestinal and Liver Physiology. 2002;283(1):G16-26.

175. 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.

176. Nguyen HN, Silny J, Matern S. Multiple intraluminal electrical impedancometry for recording of upper gastrointestinal motility: current results and further implications. American Journal of Gastroenterology. 1999;94(2):306-17.

177. Pavic I, Babic I, Cepin Bogovic J, Hojsak I. The Importance of combined 24-hour multichannel intraluminal impedance–pH monitoring in the evaluation of children with suspected laryngopharyngeal reflux. Clin Otolaryngol. 2017;42:544–9.

178. Singendonk M, Salvatore F, Tabbers M, Benninga M, Vandenplas Y. Multichannel Intraluminal Impedance and pH Monitoring (pH-MII) in Infants and Children. Gastroesophageal Reflux in Children: Springer International Publishing 2017. p. 89-110.

179. Van Wijk MP, Benninga MA, Omari TI. Role of the multichannel intraluminal impedance technique in infants and children. Journal of Pediatric Gastroenterology and Nutrition. 2009;48(1):2-12.

180. Singendonk MMJ, Oors JM, Bredenoord AJ, Omari TI, van der Pol RJ, Smits MJ, et al. Objectively diagnosing rumination syndrome in children using esophageal pH-impedance and manometry. Neurogastroenterol Motil. 2017;29(5).

181. Sifrim D, Castell D, Dent J, Kahrilas PJ. Gastro-oesophageal reflux monitoring: review and consensus report on detection and definitions of acid, non-acid, and gas reflux. Gut. 2004;53(7):1024-31.

182. Omari T, Ferris L, Dejaeger E, Tack J, Vanbeckevoort D, Rommel N. Upper esophageal sphincter impedance as a marker of sphincter opening diameter. American Journal of Physiology - Gastrointestinal and Liver Physiology. 2012;302(9):G909-13.

183. 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. Neurogastroenterology & Motility. 2009;21(3):244-52.

184. Ferris L, King S, McCall L, Rommel N, Scholten I, Teague W, et al. Piecemeal deglutition and the implications for pressure impedance dysphagia assessment in pediatrics. Journal of Pediatric Gastroenterology and Nutrition. 2018;67(6):713-9.

185. Rommel N, Selleslagh M, Hoffman I, Smet M, Davidson G, Tack J, et al. Objective assessment of swallow function in children with suspected aspiration using pharyngeal automated impedance manometry. Journal of Pediatric Gastroenterology and Nutrition. 2014;58(6):789-94.

186. Singendonk M, Kritas S, Cock C, Ferris L, McCall L, Rommel N, et al. Pressure-flow characteristics of normal and disordered esophageal motor patterns. Journal of Pediatrics. 2015;166(3):690-6.

187. Singendonk M, Omari T, Rommel N, Van Wijk M, Benninga M, Rosen R, et al. Novel pressure-impedance parameters for evaluating esophageal function in pediatric Achalasia. Journal of Pediatric Gastroenterology and Nutrition. 2018;66(1):37-42.

188. Jones CA, Knigge MA, McCulloch TM. Speech pathologist practice patterns for evaluation and management of suspected cricopharyngeal dysfunction. Dysphagia. 2014;29(3):332-9.

189. Knigge MA, Marvin S, Thibeault SL. Safety and tolerability of pharyngeal high-resolution manometry. American Journal of Speech-Language Pathology. 2019;28(1):43-52.

190. Lee T, Park JH, Sohn C, Yoon KJ, Lee Y-T, Park JH, et al. Failed deglutitive upper esophageal sphincter relaxation is a risk factor for aspiration in stroke patients with oropharyngeal dysphagia. Journal of Neurogastroenterology and Motility. 2017;23(1):34-40.

191. 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. Diseases of the Esophagus. 2014;27(3):220-9.

192. Omari TI, Ciucci M, Gozdzikowska K, Hernández 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;35(2):281-95.

193. Park C-H, Kim D-K, Lee Y-T, Yi Y. Quantitative analysis of swallowing function between dysphagia patients and healthy subjects using high-resolution manometry. Annals of Rehabilitation Medicine. 2017;41(5):776-85.

194. Park D, Oh Y, Ryu JS. Findings of abnormal videofluoroscopic swallowing study identified by high-resolution manometry parameters. Archives of Physical Medicine and Rehabilitation. 2016;97(3):421-8.

195. 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.

196. Cook I, Dodds W, Dantas RO, Massey B, Kern MK, Lang IM, et al. Opening mechanism of the human upper esophageal sphincter. American Journal of Physiology - Gastrointestinal and Liver Physiology. 1989;257(5):G748-59.

197. Dantas RO, Kern MK, Massey BT, Dodds WJ, Kahrilas PJ, Brasseur JG, et al. Effect of swallowed bolus variables on oral and pharyngeal phases of swallowing. American Journal of Physiology - Gastrointestinal and Liver Physiology. 1990;258(5 Pt 1):G675-G81.

198. Jacob P, Kahrilas PJ, Logemann JA, Shah V, Ha T. Upper esophageal sphincter opening and modulation during swallowing. Gastroenterology. 1989;97(6):1469-78.

199. Kahrilas PJ, Lin S, Chen J, Logemann JA. Oropharyngeal accommodation to swallow volume. Gastroenterology. 1996;111(2):297-306.

200. 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.

201. Doeltgen SH, Ong E, Scholten I, Cock C, Omari T. Biomechanical quantification of Mendelsohn maneuver and effortful swallowing on pharyngoesophageal function. Otolaryngology - Head and Neck Surgery. 2017;157(5):816-23.

202. Chen CL, Yi CH, Chou aSB, Liu TT. Esophageal solid bolus transit: studies using combined multichannel intraluminal impedance and manometry in healthy volunteers. Diseases of the Esophagus. 2013;26(1):91-6.

203. Cook IJ. Combined pharyngeal impedance-manometry: has it finally come of age? Clinical Gastroenterology and Hepatology. 2011;9(10):813-5.

204. Myers JC, Nguyen NQ, Jamieson GG, Van't Hek JE, Ching K, Holloway RH, et al. Susceptibility to dysphagia after fundoplication revealed by novel automated impedance manometry analysis. Neurogastroenterology & Motility. 2012;24(9):812-e393.

205. 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.

206. Omari T, Tack J, Rommel N. Impedance as an adjunct to manometric testing to investigate symptoms of dysphagia: what it has failed to do and what it may tell us in the future. United European Gastroenterology Journal. 2014;2(5):355-66.

207. Omari TI, Dejaeger E, Tack J, Vanbeckevoort D, Rommel N. An impedance-manometry based method for non-radiological detection of pharyngeal postswallow residue. Neurogastroenterology & Motility. 2012;24(7):e277-84.

208. Rommel N, Omari TI, Selleslagh M, Kritas S, Cock C, Rosan R, et al. High-resolution manometry combined with impedance measurements discriminates the cause of dysphagia in children. European Journal of Pediatrics. 2015;174(12):1629-37.

209. 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. 2017;12(2):110-5.

210. 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. Neurogastroenterology & Motility. 2018;30(12):e13481.

211. 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.

212. May NH, Davidson KW, Pearson WG, O'Rourke AK. Pharyngeal swallowing mechanics associated with upper esophageal sphincter pressure wave. Head and Neck. 2019;42(3):467-75.

213. Leonard R, Kendall K. Dysphagia assessment and treatment planning: a team approach. Fourth ed. San Diego: Plural Publishing; 2018 Mar 9. 409 p.

214. 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. Journal of Speech, Language, and Hearing Research. 2014;57(3):831-36.

215. Omari T, Savilampi J, Kokkinn K, Schar M, Lamvik K, Doeltgen S, et al. The reliability of pharyngeal HRMI for derivation of measures of swallowing function in healthy volunteers. International Journal of Otolaryngology. 2016:1-8.

216. 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. 2019;22(4):195-203.

217. 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.

218. Ertekin C, Aydogdu I. Electromyography of human cricopharyngeal muscle of the upper esophageal sphincter. Muscle & Nerve. 2002;26(6):729-39.

219. 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. Frontiers in Systems Neuroscience. 2015;8(Jan 7):1-18.

220. Jadcherla SR. Advances with neonatal aerodigestive science in the pursuit of safe swallowing in infants: invited review. Dysphagia. 2017;32(1):15-26.

221. Jadcherla SR, Shubert TR, Malkar MB, Sitaram S, Moore RK, Wei L, et al. Gestational and postnatal modulation of esophageal sphincter reflexes in human premature neonates. Pediatric Research. 2016;78(5):540-6.

222. Hasenstab KA, Sitaram S, Lang I, Shaker R, Jadcherla SR. Maturation modulates pharyngeal-stimulus provoked pharyngeal and respiratory rhythms in human infants. Dysphagia. 2018;33(1):63-75.

223. Hasenstab KA, Jadcherla SR. Respiratory events in infants presenting with apparent life threatening events: is there an explanation from esophageal motility? Journal of Pediatrics. 2014;165(2):250-5.e1.

224. Jean A. Brain stem control of swallowing: neuronal network and cellular mechanisms. Physiological Reviews. 2001;81(2):929-69.

225. Cock C, Jones C, Hammer M, Omari T, McCulloch T. Modulation of upper esophageal sphincter (UES) relaxation and opening during volume swallowing. Dysphagia. 2017;32(2):216-24.

226. Cook IJ, Dodds WJ, Dantas RO, Kern MK, Massey BT, Shaker R, et al. Timing of videofluoroscopic, manometric events, and bolus transit during the oral and pharyngeal phases of swallowing. Dysphagia. 1989;4(1):8-15.

227. Dodds WJ, Stewart ET, Logemann JA. Physiology and radiology of the normal oral and pharyngeal phases of swallowing. American Journal of Roentgenology. 1990;154(5):953-63.

228. Bardan E, Kern M, Arndorfer RC, Hofmann C, Shaker R. Effect of aging on bolus kinematics during the pharyngeal phase of swallowing. American Journal of Physiology - Gastrointestinal and Liver Physiology. 2006;290(3):G458-65.

229. Carlson DA, Pandolfino JE. High-resolution manometry in clinical practice. Gastroenterology & Hepatology. 2015;11(6):374-84.

230. Kuhn MA, Belafsky PC. Management of cricopharyngeus muscle dysfunction. Otolaryngologic Clinics of North America. 2013;46(6):1087-99.

231. Savarino E, de Bortoli N, Bellini M, Galeazzi F, Ribolsi M, Salvador R, et al. Practice guidelines on the use of esophageal manometry – A GISMAD-SIGE-AIGO medical position statement. Digestive and Liver Disease. 2016;48(10):1124-35.

232. Shaker R, Easterling C, Belafsky PC, Postma GN. Manual of diagnostic and therapeutic techniques for disorders of deglutition: Springer Science & Business Media; 2012 Sep 14. 421 p.

233. 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. 2017;128(6):1328-34.

234. Rosen SP, Abdelhalim SM, Jones CA, McCulloch TM. Effect of body position on pharyngeal swallowing pressures using high-resolution manometry. Dysphagia. 2017;33(3):389-98.

235. Lamvik K, Macrae P, Doeltgen S, Collings A, Huckabee M-L. Normative data for pharyngeal pressure generation during saliva, bolus, and effortful saliva swallowing across age and gender. Speech, Language and Hearing. 2014;17(4):210-5.

236. Jadcherla SR, Prabhakar V, Hasenstab KA, Nawaz S, Das J, Kern M, et al. Defining pharyngeal contractile integral during high-resolution manometry in neonates: a neuromotor marker of pharyngeal vigor. Pediatric Research. 2018;84(3):341-7.

237. Omari TI, Dejaeger E, Tack J, Van Beckevoort D, Rommel N. Effect of bolus volume and viscosity on pharyngeal automated impedance manometry variables derived for broad dysphagia patients. Dysphagia. 2013;28(2):146-52.

238. 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.

239. Zhang T, Szczesniak M, Maclean J, Bertrand P, Wu PI, Omari T, et al. Biomechanics of pharyngeal deglutitive function following total laryngectomy. Otolaryngology - Head and Neck Surgery. 2016;155(2):295-302.

240. 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. Neurogastroenterology & Motility. 2016;28(2):225-33.

241. 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. Neurogastroenterology & Motility. 2018;30(5):e13277.

242. Knigge M, Thibeault S. Swallowing outcomes after cricopharyngeal myotomy: a systematic review. Head and Neck. 2018;40(1):203-12.

243. Marchica C, Zawawi F, Daniel SJ. Management of cricopharyngeal achalasia in an 8-month child using endoscopic cricopharyngeal myotomy. International Journal of Pediatric Otorhinolaryngology. 2017;101:137-40.

244. Mohan S, Bowe SN, Hirner LM, Zar-Kessler C, Hartnick CJ. Modified approach for pediatric external cricopharyngeal myotomy. International Journal of Pediatric Otorhinolaryngology. 2018;105:111-4.

245. Rommel N, Davidson G, Cain T, Hebbard G, Omari T. Videomanometric evaluation of pharyngo-oesophageal dysmotility in children with velocardiofacial syndrome. Journal of Pediatric Gastroenterology and Nutrition. 2008;46(1):87-91.

246. Dharmarathna I, Miles A, Allen JE. Current approaches to instrumental assessment of swallowing in children. Current Opinion in Otolaryngology & Head and Neck Surgery. 2018;26(6):349-55.

247. Gosa MM, Suiter DM, Kahane JC. Reliability for identification of a select set of temporal and physiologic features of infant swallows. Dysphagia. 2015;30(3):365-72.

248. Sales AVMN, Giacheti CM, Cola PC, Silva RGD. Qualitative and quantitative analysis of oropharyngeal swallowing in Down syndrome. Sociedade Brasileira de Fonoaudiologia 2017;29(6).

249. Omari TI, Dejaeger E, Tack J, Vanbeckevoort D, Rommel N. An impedance-manometry based method for non-radiological detection of pharyngeal postswallow residue. Neurogastroenterology & Motility. 2012;24(7):e277-e84.

250. Pal A, Williams RB, Cook IJ, Brasseur JG. Intrabolus pressure gradient identifies pathological constriction in the upper esophageal sphincter during flow. American Journal of Physiology - Gastrointestinal and Liver Physiology. 2003;285(5):G1037-48.

251. 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. International Journal of Otolaryngology. 2015;2015:1-7.

252. Bowles J, Jnah A. Infants with technology dependence. Outcomes of Neonatal Care. 2016;16(6):424-9.

253. Kelly MM. The medically complex premature infant in primary care. Journal of Pediatric Health Care. 2006;20(6):367-73.

254. Schaen-Heacock NE, Jones CA, McCulloch TM. Pharyngeal swallowing pressures in patients with radiation-associated dysphagia. Dysphagia. 2020.

255. Kahrilas PJ, Dodds WJ, Dent J, Logemann JA, Shaker R. Upper esophageal sphincter function during deglutition. Gastroenterology. 1988;95:52-62.

256. Omari T, Ferris L, Cajander P, Cock C, Doeltgen S, Rommel N, et al. A standardized test medium to detect bolus-related modulation during high-resolution pharyngeal manometry. Gastroenterology. 2018;154(6):S-982.

257. Ferris L, Doeltgen S, Cock C, Rommel N, Schar M, Carrion S, et al. Modulation of pharyngeal swallowing by bolus volume and viscosity. American Journal of Physiology - Gastrointestinal and Liver Physiology. 2021;320(1):G43-G53.

258. 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.

259. 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. Annals of Otology, Rhinology and Laryngology. 2015;124(7):537-44.

260. Ertekin C, Aydogdu I. Neurophysiology of swallowing. Clinical Neurophysiology. 2003;114(12):2226-44.

261. Shaker R, Belafsky P, Postma G, Easterling C. Principles of deglutition: a multidisciplinary text for swallowing and its disorders. New York: Springer Science & Business Media; 2013.

262. Alvarez-Berdugo D, Rofes L, Casamitjana JF, Padrón A, Quer M, Clavé P. Oropharyngeal and laryngeal sensory innervation in the pathophysiology of swallowing disorders and sensory stimulation treatments. Annals of the New York Academy of Sciences. 2016;1380(1):104-20.

263. Lazarus CL, Logemann JA, Rademaker AW, Kahrilas PJ, Pajak T, Lazar R, et al. Effects of bolus volume, viscosity, and repeated swallows in nonstroke subjects and stroke patients. Archives of Physical Medicine and Rehabilitation. 1993;74(10):1066-70.

264. Chen WH, Omari TI, Holloway RH, Checklin H, Dent J. A comparison of micromanometric and standard manometric techniques for recording of oesophageal motility. Neurogastroenterology & Motility. 1998;10(3):253-62.

265. Lydon SB, Dodds WJ, Hogan WJ, Arndorfer RC. The effect of manometric assembly diameter on intraluminal esophageal pressure recording. American Journal of Digestive Diseases. 1975;20(10):968-70.

266. Xiang X, Tu L, Zhang X, Xie X, Hou X. Influence of the catheter diameter on the investigation of the esophageal motility through solid-state high-resolution manometry. Diseases of the Esophagus. 2013;26(7):661-7.

267. Doeltgen SH, Omari TI, Savilampi J. Remifentanil alters sensory neuromodulation of swallowing in healthy volunteers: quantification by a novel pressure-impedance analysis. American Journal of Physiology - Gastrointestinal and Liver Physiology. 2016;310(11):G1176-G82.

268. Omari TI, Papathanasopoulos A, Dejaeger E, Wauters L, Scarpellini E, Vos R, et al. Reproducibility and agreement of pharyngeal automated impedance manometry with videofluoroscopy. Clinical Gastroenterology and Hepatology. 2011;9(10):862-7.

269. Gumbley F, Huckabee ML, Doeltgen SH, Witte U, Moran C. Effects of bolus volume on pharyngeal contact pressure during normal swallowing. Dysphagia. 2008;23(3):280-5.

270. Nascimento WV, Cassiani RA, Santos CM, Dantas RO, Article O. Effect of bolus volume and consistency on swallowing events duration in healthy subjects. Journal of Neurogastroenterology and Motility. 2015;21(1):78-82.

271. Humbert IA, Lokhande A, Christopherson H, German R, Stone A. Adaptation of swallowing hyo-laryngeal kinematics is distinct in oral vs. pharyngeal sensory processing. Journal of Applied Physiology. 2012;112(10):1698-705.

272. Nagai T. The occurrence and ultrastructure of a mechanoreceptor in the human cricopharyngeus muscle. European Archives of Oto-Rhino-Laryngology. 1991;248(3):144-6.

273. Steele C, Miller AJ. Sensory input pathways and mechanisms in swallowing: a review. Dysphagia. 2010;25(4):323-33.

274. Knigge MA, Thibeault S. Relationship between tongue base region pressures and vallecular clearance. Dysphagia. 2016;31(3):391-7.

275. Regan J. Impact of sensory stimulation on pharyngo-esophageal swallowing biomechanics in adults with dDysphagia: a high-resolution manometry study. Dysphagia. 2020(1):1-9.

276. Lee TH, Lee JS, Kim WJ. High resolution impedance manometric findings in dysphagia of Huntington's disease. World Journal of Gastroenterology. 2012;18(14):1695-9.

277. Schar MS, Omari TI, Fraser RJ, Bersten AD, Bihari S. Disordered swallowing associated with prolonged oral endotracheal intubation in critical illness. Intensive Care Medicine. 2020;46(1):140-2.

278. Nguyen NQ, Holloway RH, Smout AJ, Omari TI. Automated impedance-manometry analysis detects esophageal motor dysfunction in patients who have non-obstructive dysphagia with normal manometry. Neurogastroenterology & Motility. 2013;25(3):238-45, e164.

279. Robbins J, Nicosia M, Hind JA, Gill GD, Blanco R, Logemann J. Defining physical properties of fluids for dysphagia evaluation and treatment. SIG 13 Perspectives on Swallowing and Swallowing Disorders (Dysphagia). 2002;11(2):16-9.

280. Newman R, Vilardell N, Clavé P, Speyer R. Effect of bolus viscosity on the safety and efficacy of swallowing and the kinematics of the swallow response in patients with oropharyngeal dysphagia: white paper by the European Society for Swallowing Disorders (ESSD). Dysphagia. 2016;31(2):232-49.

281. Bolivar-Prados M, Rofes L, Arreola V, Guida S, Nascimento WV, Martin A, et al. Effect of a gum-based thickener on the safety of swallowing in patients with poststroke oropharyngeal dysphagia. Neurogastroenterology & Motility. 2019;31(11):1-11.

282. Cock C, Omari T. Systematic review of pharyngeal and esophageal manometry in healthy or dysphagic older persons (>60 years). Geriatrics. 2018;3(4):67.

283. Butler SG, Stuart A, Castell D, Russell G, 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(1).

284. Ryu JSo, 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. Journal of Neurogastroenterology and Motility. 2015;22(2):231-9.

285. 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.

286. Dakkak M, Bennett JR. A new dysphagia score with objective validation. Journal of Clinical Gastroenterology. 1992;14(2):99-100.

287. 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(4):678-87.

288. 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. Archives of Physical Medicine and Rehabilitation. 2018;99(5):934-44.

289. Cook IJ, Weltman MD, Wallace K, Shaw DW, McKay E, Smart RC, et al. Influence of aging on oral-pharyngeal bolus transit and clearance during swallowing: scintigraphic study. American Journal of Physiology - Gastrointestinal and Liver Physiology. 1994;266(6 29-6):972-7.

290. 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):G1057-63.

291. Nativ-Zeltzer N, Belafsky PC, Bayoumi A, Kuhn MA. Volitional control of the upper esophageal sphincter with high-resolution manometry driven biofeedback. Laryngoscope Investigative Otolaryngology. 2019;4(2):264-8.

292. Lang IM, Medda BK, Shaker R. Characterization and mechanism of the esophago-esophageal contractile reflex of the striated muscle esophagus. American Journal of Physiology - Gastrointestinal and Liver Physiology. 2019;317(3):G304-G13.

293. Lin T, Xu G, Dou Z, Lan Y, Yu F, Jiang L. Effect of bolus volume on pharyngeal swallowing assessed by high-resolution manometry. Physiology & Behavior. 2014;128:46-51.

294. Hanson B. A review of diet standardization and bolus rheology in the management of dysphagia. Current Opinion in Otolaryngology & Head and Neck Surgery. 2016;24(3):183-90.

295. Ong JJX, Steele CM, Duizer LM. Sensory characteristics of liquids thickened with commercial thickeners to levels specified in the International Dysphagia Diet Standardization Initiative (IDDSI) framework. Food Hydrocolloids. 2018;79:208-17.

296. Ong JJX, Steele CM, Duizer LM. Challenges to assumptions regarding oral shear rate during oral processing and swallowing based on sensory testing with thickened liquids. Food Hydrocolloids. 2018;84:173-80.

297. Qazi WM, Ekberg O, Wiklund J, Kotze R, Stading M. Assessment of the food-swallowing process using bolus visualisation and manometry simultaneously in a device that models human swallowing. Dysphagia. 2019;34(6):821-33.

298. Tomsen N, Alvarez-Berdugo D, Rofes L, Ortega O, Arreola V, Nascimento W, et al. A randomized clinical trial on the acute therapeutic effect of TRPA1 and TRPM8 agonists in patients with oropharyngeal dysphagia. Neurogastroenterology & Motility. 2020;32(6):e13821.

299. Singendonk M, Rommel N, Omari T, Benninga M, van Wijk M. Upper gastrointestinal motility: prenatal development and problems in infancy. Nature Reviews: Gastroenterology & Hepatology. 2014;11(9):545-55.

300. Benfer KA, Weir KA, Bell KL, Ware RS, Davies PSW, Boyd RN. Clinical signs suggestive of pharyngeal dysphagia in preschool children with cerebral palsy. Research in Developmental Disabilities. 2015;38:192-201.

301. van den Engel-Hoek L, Erasmus CE, van Hulst KCM, Arvedson JC, de Groot IJM, de Swart BJM. Children with central and peripheral neurologic disorders have distinguishable patterns of dysphagia on videofluoroscopic swallow study. Journal of Child Neurology. 2014;29(5):646-53.

302. Jadcherla SR, Stoner E, Gupta A, Bates DG, Fernandez S, Di Lorenzo C, et al. Evaluation and management of neonatal dysphagia: impact of pharyngoesophageal motility studies and multidisciplinary feeding strategy. Journal of Pediatric Gastroenterology and Nutrition. 2009;48(2):186-92.

303. Qureshi MA, Vice FL, Taciak VL, Bosma JF, Gewolb IH. Changes in rhythmic suckle feeding patterns in term infants in the first month of life. Developmental Medicine and Child Neurology. 2002;44(1):34-9.

304. Ertekin C, Aydoğdu I, Yüceyar N. Piecemeal deglutition and dysphagia limit in normal subjects and in patients with swallowing disorders. Journal of Neurology, Neurosurgery and Psychiatry. 1996;61(5):491-6.

305. Mahoney L, Rosen R. Feeding difficulties in children with esophageal atresia. Paediatric Respiratory Reviews. 2016;19:21-7.

306. Rommel N, Rayyan M, Scheerens C, Omari T. The potential benefits of applying recent advances in esophageal motility testing in patients with esophageal atresia. Frontiers in Pediatrics. 2017;5(June):1-7.

307. Arvedson JC. Feeding children with cerebral palsy and swallowing difficulties. European Journal of Clinical Nutrition. 2013;67(S2):S9-12.

308. da Costa SP, van den Engel-Hoek L, Bos AF. Sucking and swallowing in infants and diagnostic tools. Journal of Perinatology. 2008;28(4):247-57.

309. Flanagan L. The validity of a three-part criteria for differentiating between delayed pharyngeal swallow and premature spillage secondary to poor oro-lingual control on videofluoroscopy. Christchurch, New Zealand: University of Canterbury; 2007.

310. Morton R, Minford J, Ellis R, Pinnington LL. Aspiration with dysphagia: the interaction between oropharyngeal and respiratory impairments. Dysphagia. 2002;17(3):192-6.

311. Crary MA, Mann GDC, Groher ME. Initial psychometric assessment of a functional oral intake scale for dysphagia in stroke patients. Archives of Physical Medicine and Rehabilitation. 2005;86(8):1516-20.

312. Hunt PS, Connell AM, Smiley TB. The cricopharyngeal sphincter in gastric reflux. Gut. 1970;11(4):303-6.

313. Alkan Z, Demir a, Yigit O, Adatepe T, Kesici B, Kocak I, et al. Cricopharyngeal muscle electromyography findings in patients with gastroesophageal reflux disease. Otolaryngology - Head and Neck Surgery. 2012;147(2):295-301.

314. Stevenson RD, Allaire JH. The development of normal feeding and swallowing. Pediatric Clinics of North America. 1991;38(6):1439-53.

315. Huda W. Effective doses to adult and pediatric patients. Pediatr Radiol. 2002;32(4):272-9.

316. Cook IJ, Dent J, Shannon S, Collins SM. Measurement of upper esophageal sphincter pressure. Gastroenterology. 1987;93(3):526-32.

317. 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.

318. Skeat J, Perry A. Outcome measurement in dysphagia: not so hard to swallow. Dysphagia. 2005;20(2):113-22.

319. Singendonk MMJ, Kritas S, Cock C, Ferris L, McCall L, Rommel N, et al. Applying the Chicago Classification criteria of esophageal motility to a pediatric cohort: effects of patient age and size. Neurogastroenterology & Motility. 2014;26(9):1333-41.

320. Benfer KA, Weir KA, Bell KL, Ware RS, Davies PSW, Boyd RN. Oropharyngeal dysphagia and cerebral palsy. Pediatrics. 2017;140(6):e20170731-e.

321. Caselli TB, Lomazi EA, Montenegro MAS, Bellomo-Brandão MA. Assessment of nutritional status of children and adolescents with spastic quadriplegic cerebral palsy. Arquivos de Gastroenterologia. 2017;54(3):201-5.

322. Mishra A, Malandraki GA, Sheppard JJ, Gordon AM, Levy ES, Troche MS. Voluntary cough and clinical swallow function in children with spastic cerebral palsy and healthy controls. Dysphagia. 2019;34(2):145-54.

323. Yoon KJ, Park JH, Park JH, Jung IS. Videofluoroscopic and manometric evaluation of pharyngeal and upper esophageal sphincter function during swallowing. Journal of Neurogastroenterology and Motility. 2014;20(3):352-61.

324. 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.

325. Mittal RK, Muta K, Ledgerwood-Lee M, Zifan A. Relationship between distension-contraction waveforms during esophageal peristalsis: effect of bolus volume, viscosity, and posture. American Journal of Physiology - Gastrointestinal and Liver Physiology. 2020;319(4):G454-G61.

326. Sharma T, Mei L, Jiao H, Shaker R. Nadir UES relaxation and hypopharyngeal intra Bolus pressures are more sensitive to consistency and viscosity challenge than pharyngeal peristalsis parameters measured by high resolution manometry. Gastroenterology. 2014;146(5):S-78.

327. Duncan DR, Larson K, Rosen RL. Clinical aspects of thickeners for pediatric gastroesophageal reflux and oropharyngeal dysphagia. Current Gastroenterology Reports. 2019;21(7).

328. Rommel N, Omari T. Abnormal pharyngoesophageal function in infants and young children: diagnosis with high-resolution manometry. Journal of Pediatric Gastroenterology and Nutrition. 2011;52(S1):S29-30.

329. Ruark JL, McCullough GH, Peters RL, Moore CA. Bolus consistency and swallowing in children and adults. Dysphagia. 2002;17(1):24-33.

330. 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.

331. Weir K, McMahon S, Barry L, Masters IB, Chang aB. Clinical signs and symptoms of oropharyngeal aspiration and dysphagia in children. European Respiratory Journal. 2009;33(3):604-11.

332. Jadcherla SR, Chan CY, Moore R, Fernandez S, Shaker R. Physiology of esophageal sensorimotor malfunctions in neonatal neurological illness. American Journal of Physiology - Gastrointestinal and Liver Physiology. 2013;304(6):G574-82.

333. Barnes MA, Ho AS, Malhotra PS, Koltai PJ, Messner A. The use of botulinum toxin for pediatric cricopharyngeal achalasia. International Journal of Pediatric Otorhinolaryngology. 2011;75(9):1210-4.

334. Brooks A, Millar AJW, Rode H. The surgical management of cricopharyngeal achalasia in children. International Journal of Pediatric Otorhinolaryngology. 2000;56(1):1-7.

335. Erdeve O, Kologlu M, Saygili B, Atasay B, Arsan S. Primary cricopharyngeal achalasia in a newborn treated by balloon dilatation: a case report and review of the literature. International Journal of Pediatric Otorhinolaryngology. 2007;71(1):165-8.

336. Scholes Ma, McEvoy T, Mousa H, Wiet GJ. Cricopharyngeal achalasia in children: botulinum toxin injection as a tool for diagnosis and treatment. Laryngoscope. 2014;124(6):1475-80.

337. Türer ÖB, Demir N, Ciecieraga T, Günaydın RÖ, Soyer T. Assessment of pediatric cricopharyngeal achalasia with high resolution manometry. Turkish Journal of Pediatrics. 2019;61(5):804-9.

338. Lee T, Park JH, Sohn C, Yoon KJ, Lee Y-T, Park JH, et al. Failed deglutitive upper esophageal sphincter relaxation is a risk factor for aspiration in stroke patients with oropharyngeal dysphagi. Journal of Neurogastroenterology and Motility. 2017;23(1):34-40.

339. Al-Toubi AK, Doeltgen SH, Daniels SK, Corey DM, Huckabee ML. Pharyngeal pressure differences between four types of swallowing in healthy participants. Physiology & Behavior. 2015;140:132-8.

340. Bülow M, Olsson R, Ekberg O. Supraglottic swallow, effortful swallow, and chin tuck did not alter hypopharyngeal intrabolus pressure in patients with pharyngeal dysfunction. Dysphagia. 2002;17(3):197-201.

341. Battel I, Calvo I, Walshe M. Interventions involving biofeedback to improve swallowing in people with parkinson disease and dysphagia: a systematic review. Archives of Physical Medicine and Rehabilitation. 2021;102(2):314-22.

342. Jadcherla SR, Shubert TR, Gulati IK, Jensen PS, Wei L, Shaker R. Upper and lower esophageal sphincter kinetics are modified during maturation effect of pharyngeal stimulus in premature infants. Pediatric Research. 2015;77(1):99-106.

343. Rayyan M, Omari T, Debeer A, Allegaert K, Rommel N. Characterization of esophageal motility and esophagogastric junction in preterm infants with bronchopulmonary dysplasia. Neurogastroenterol Motil. 2020;32(7):e13849.

344. Roué J-M, Kuhn P, Lopez Maestro M, Maastrup RA, Mitanchez D, Westrup B, et al. Eight principles for patient-centred and family-centred care for newborns in the neonatal intensive care unit. Archives of Disease in Childhood: Fetal and Neonatal Edition. 2017;102(4):F364-F8.

345. Flory N, Salazar GMM, Lang EV. Hypnosis for acute distress management during medical procedures. International Journal of Clinical and Experimental Hypnosis. 2007;55(3):303-17.

346. Liossi C, White P, Hatira P. A randomized clinical trial of a brief hypnosis intervention to control venepuncture-related pain of paediatric cancer patients. Pain. 2009;142(3):255-63.

347. McBride JJ, Vlieger AM, Anbar RD. Hypnosis in paediatric respiratory medicine. Paediatric Respiratory Reviews. 2014;15(1):82-5.

348. Szanto T. Say Less, Show More NSW Agency for Clinical Innovation2021 [Available from: https://aci.health.nsw.gov.au/resources/intellectual-disability/childrens-services/say-less-show-more

349. Isaac A, El-Hakim H. Type 1 laryngeal cleft and feeding and swallowing difficulties in infants and toddlers: a review. Clinical Otolaryngology. 2019;44(2):107-13.

350. Aires MM, Marinho CB, Vasconcelos SJD. Surgical interventions for pediatric unilateral vocal fold paralysis: a systematic review and meta-analysis. International Journal of Pediatric Otorhinolaryngology. 2021;141:110553.

351. Scott BL, Lam D, Macarthur C. Laryngomalacia and swallow dysfunction. Ear, Nose, & Throat Journal. 2019;98(10):613-6.

352. Krishnan U, Faure C. Update on oesophageal atresia-tracheoesophageal fistula. Frontiers in Pediatrics. 2017;5(October):190.

353. François K, Panzer J, De Groote K, Vandekerckhove K, De Wolf D, De Wilde H, et al. Early and late outcomes after surgical management of congenital vascular rings. European Journal of Pediatrics. 2017;176(3):371-7.

354. Ojo O, Keaveney E, Wang X-H, Feng P. The effect of enteral tube feeding on patients' health-related quality of life: a systematic review. Nutrients. 2019;11(5):1046.

355. Benfer KA, Weir KA, Bell KL, Ware RS, Davies PSW, Boyd RN. Oropharyngeal dysphagia and cerebral palsy. Pediatrics. 2017;140(6):e20170731.

356. Bastos JL, Peres MA, Peres KG, Barros AJD. Infant growth, development and tooth emergence patterns: a longitudinal study from birth to 6 years of age. Archives of Oral Biology. 2007;52(6):598-606.

357. Jones CA. Physiology of normal swallow. In: McMurray JS, Hoffman MR, Braden MN, editors. Multidisciplinary management of pediatric voice and swallowing disorders: Springer International Publishing; 2020. p. 135-42.

358. Fiadjoe JE, Litman RS, Serber JF, Stricker PA, Coté CJ. The pediatric airway. A practice of anesthesia for infants and children. 6th ed: Elsevier; 2019. p. 297-339.e21.

359. Shaker R. Reflex interaction of pharynx, esophagus, and airways. GI Motility online. 2006.

360. Lau C. Development of suck and swallow mechanisms in infants. Annals of Nutrition and Metabolism. 2015;66(Suppl. 5):7-14.

361. Gewolb IH, Vice FL, Schweitzer-Kenney EL, Taciak VL, Bosma JF. Developmental patterns of rhythmic suck and swallow in preterm infants. Developmental Medicine and Child Neurology. 2007;43(1):22-7.

362. Mohad V, Hirsch H, Thibeault SL. Embryonic and histologic development of the vocal tract. In: McMurray JS, Hoffman MR, Braden MN, editors. Multidisciplinary management of pediatric voice and swallowing disorders: Springer International Publishing; 2020. p. 63-72.

363. Miller AJ. The neurobiology of swallowing and dysphagia. Developmental Disabilities Research Reviews. 2008;14(2):77-86.

364. Delaney AL, Arvedson JC. Development of swallowing and feeding: Prenatal through first year of life. Developmental Disabilities Research Reviews. 2008;14(2):105-17.

365. Kelly BN, Huckabee ML. Measuring breathing and swallowing coordination in human infants using the Kay Elemetrics Swallowing Workstation. University of Washington; 2003. p. 1-9.

366. Jafari S, Prince RA, Kim DY, Paydarfar D. Sensory regulation of swallowing and airway protection: a role for the internal superior laryngeal nerve in humans. Journal of Physiology. 2003;550(1):287-304.

367. Parano E, Uncini A, De Vivo DC, Lovelace RE. Electrophysiologic correlates of peripheral nervous system maturation in infancy and childhood. Journal of Child Neurology. 1993;8(4):336-8.

368. Matsuo K, Palmer JB. Anatomy and physiology of feeding and swallowing: normal and abnormal. Physical Medicine and Rehabilitation Clinics of North America. 2008;19(4):691-707.

369. Evans Morris S, Dunn Klein M. Pre-feeding skills: a comprehensive resource for mealtime development. 2nd ed2000.

370. Jadcherla SR, Gupta A, Stoner E, Fernandez S, Shaker R. Pharyngeal swallowing: defining pharyngeal and upper esophageal sphincter relationships in human neonates. Journal of Pediatrics. 2007;151(6):597-603.

371. Jadcherla SR, Hasenstab Ka, Shaker R, Castile RG. Mechanisms of cough provocation and cough resolution in neonates with bronchopulmonary dysplasia. Pediatric Research. 2015;78(4):462-9.

372. Lang IM. Brain stem control of the phases of swallowing. Dysphagia. 2009;24(3):333-48.

373. Shaker R, Ren J, Xie P, Lang IM, Bardan E, Sui Z. Characterization of the pharyngo-UES contractile reflex in humans. American Journal of Physiology - Gastrointestinal and Liver Physiology. 1997;273(4):G854-8.

374. Polverino M, Polverino F, Fasolino M, Andò F, Alfieri A, De Blasio F. Anatomy and neuro-pathophysiology of the cough reflex arc. Multidisciplinary Respiratory Medicine. 2012;7(1):5.

375. Weir K, McMahon S, Barry L, Ware R, Masters IB, Chang AB. Oropharyngeal aspiration and pneumonia in children. Pediatric Pulmonology. 2007;42(11):1024-31.

376. Arvedson J, Lefton-Greif MA. Pediatric videofluoroscopic swallow studies: a professional manual with caregiver guidelines: San Antonio, Tex. : Communication Skill Builders/Psychological Corporation; 1998.

377. Omari TI, Benninga MA, Barnett CP, Haslam RR, Davidson GP, Dent J. Characterization of esophageal body and lower esophageal sphincter motor function in the very premature neonate. J Pediatr. 1999;135(4):517-21.

378. Baujat G, Faure C, Zaouche A, Viarme F, Couly G, Abadie V. Oroesophageal motor disorders in Pierre Robin syndrome. J Pediatr Gastroenterol and Nutrit. 2001;32(3):297-302.

379. Baudon J-J, Renault F, Goutet J-M, Flores-Guevara R, Soupre V, Gold F, et al. Motor dysfunction of the upper digestive tract in Pierre Robin sequence as assessed by sucking- swallowing electromyography and esophageal manometry. J Pediatr. 2002:719-23.

380. Staiano A, Boccia G, Salvia G, Zappulli D, Clouse RE. Development of esophageal peristalsis in preterm and term neonates. Gastroenterology. 2007;132(5):1718-25.

381. Staiano A, Boccia G, Miele E, Clouse RE. Segmental characteristics of oesophageal peristalsis in paediatric patients. Neurogastroenterol & Motil. 2008;20(1):19-26.

382. Goldani HAS, Staiano A, Borrelli O, Thapar N, Lindley KJ. Pediatric esophageal high-resolution manometry: utility of a standardized protocol and size-adjusted pressure topography parameters. Am J Gastroenterol. 2010;105(2):460-7.

383. Morera C, Nurko S. Heterogeneity of lower esophageal sphincter function in children with achalasia. J Pediatr Gastroenterol Nutr. 2012;54(1):34-40.

384. Lemoine C, Aspirot A, Le Henaff G, Piloquet H, Lévesque D, Faure C. Characterization of esophageal motility following esophageal atresia repair using high-resolution esophageal manometry. J Pediatr Gastroenterol Nutr. 2013;56(6):609-14.

385. Rosen R, Rodriguez L, Nurko S. Pediatric rumination subtypes: A study using high-resolution esophageal manometry with impedance. Neurogastroenterol & Motil. 2017;29(5):e12998.

386. Grunder FR, Aspirot A, Faure C. High-resolution esophageal manometry patterns in children and adolescents with rumination syndrome. J Pediatr Gastroenterol Nutr. 2017;65(6):627-32.

387. Omari T, Connor F, McCall L, Ferris L, Ellison S, Hanson B, et al. A study of dysphagia symptoms and esophageal body function in children undergoing anti-reflux surgery. European Gastroenterol J. 2018;6(6):819-29.

388. Prabhakar V, Hasenstab KA, Osborn E, Wei L, Jadcherla SR. Pharyngeal contractile and regulatory characteristics are distinct during nutritive oral stimulus in preterm-born infants: Implications for clinical and research applications. Neurogastroenterol & Motil. 2019;31(8).

389. Hasenstab-Kenney KA, Bellodas Sanchez J, Prabhakar V, Lang IM, Shaker R, Jadcherla SR. Mechanisms of bradycardia in premature infants: Aerodigestive–cardiac regulatory–rhythm interactions. Physiol Rep. 2020;8(13).

390. Rayyan M, Omari T, Naulaers G, Aerts R, Allegaert K, Rommel N. Maturation of Esophageal Motility and Esophagogastric Junction in Preterm Infants. Neonatology. 2020;117(4):495-503.

Appendix 1

The Typical Development of Swallowing Anatomy and Physiology in Children

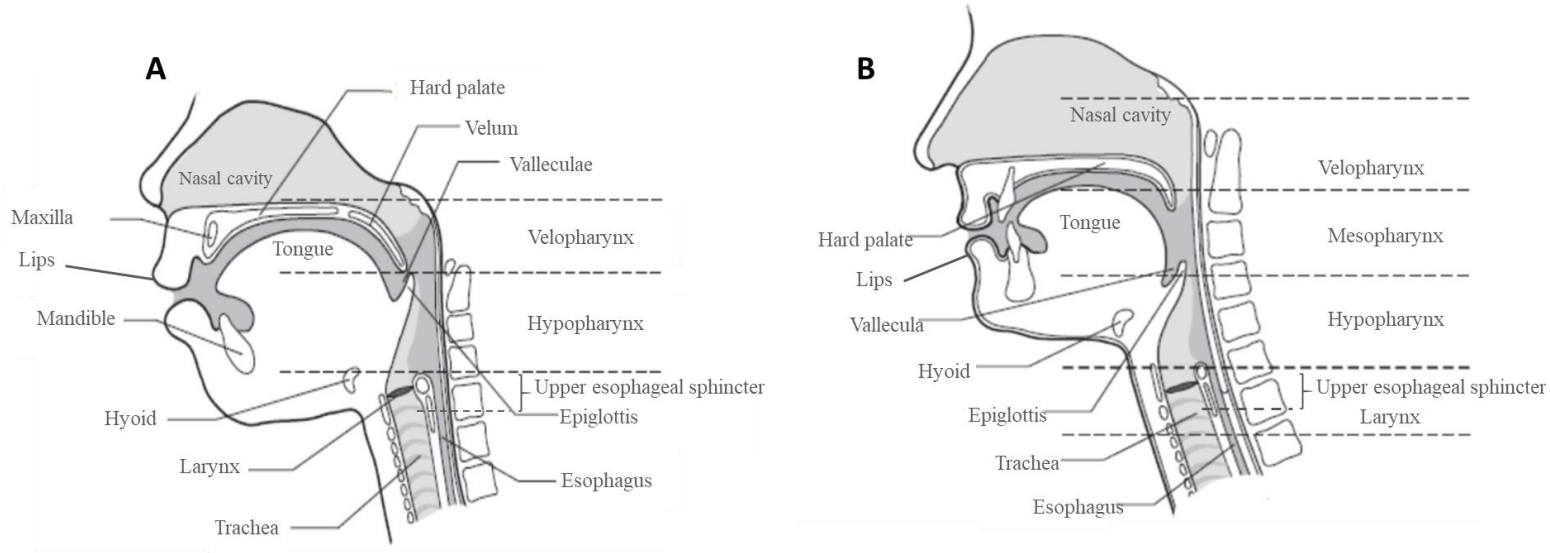
This section provides an overview of paediatric swallowing anatomy and physiology to summarise the complex processes typically involved in swallowing maturation and the changes occurring with growth and development throughout early childhood. The anatomical structures involved in swallowing are outlined first, followed by a discussion of the development of swallowing physiology, neural control of swallowing and finally, a brief overview of the main causes of disruption to the systems, which can consequently lead to OPD. There is some repetition of material owing to the complex and integrated nature of the swallowing process and the relationships in focus at any one time. This material is included as an Appendix rather than in the body of the text to ensure the interested reader is informed of this background information while enhancing readability of this thesis.

Anatomical Development of Infant Swallowing

In the early months of life, many changes occur in the anatomical structures involved in swallowing (6, 7). Positional stability of swallowing structures and airway protection during the intricate coordination of the suck-swallow-breathe pattern is achieved with the proximity of base of tongue and UOS. The infant's cheeks are padded with adipose tissue which also provides stabilisation during the sucking action (7). Over the first 6-24 months of life, this tissue gradually reduces and there is deepening of the internal space between the mandible and cheeks, referred to as the lateral sulci. With growth and development during this time, dentition also begins to emerge for mastication of different food textures. Food textures are gradually introduced from smooth, thin purees, to thicker purees, to soft foods mechanically compressed by the gums/early dentition, tongue and hard palate. Between 2-4 years of age, a range of

complex textured foods can be managed due to the structural and physiological growth that allows for adequate oral strength and coordination (356). Additionally, the size of connective tissues and cartilage in laryngeal and pharyngeal swallowing structures increases and the nasopharyngeal/velopharyngeal space becomes more acute and approaches a 90-degree angle (6). These changes lead to the pharynx becoming elongated and the mesopharyngeal space emerges, as depicted in Figure 33, image B. These anatomical changes facilitate the postural control required for swallowing in an upright position (6, 7). The anatomical structures involved in oropharyngeal swallowing are outlined below.

Figure 1. *Anatomy of Swallowing and Airway Structures*



Note. This figure demonstrates the anatomy of an infant in image A, showing the hypopharynx is positioned directly below the base of tongue. Image B depicts the anatomy of an older child with elongation of the pharyngeal space, creating the mesopharyngeal zone. Please note images were reprinted from *Pediatric Swallowing and Feeding Assessment and Management: 3rd ed, San Diego, CA: Plural Publishing; 2020, page 12 and 14, reproduced with permission*. Adjustments have been made to illustrate the upper oesophageal sphincter and labels: velopharynx, mesopharynx and hypopharynx have been included.

Oral Cavity

The oral cavity structures include the lips, mandible (jaw), maxilla, floor of mouth, cheeks, tongue, hard palate, soft palate, and anterior surfaces of the faucial arches (26, 357). The faucial arches are vertical folds of tissue, which surround the palatine tonsils, situated in the oropharyngeal region. The oropharyngeal mucosa is densely innervated to perceive a range of chemical, thermal and mechanical stimuli involved in the initiation of the pharyngeal swallowing response (261). Spanning the mandible are the floor of mouth structures. These are the mylohyoid, geniohyoid and anterior belly of the digastric muscles (7).

The oral structures are needed for the preparation and oral control of the ingested food/fluid, referred to as the bolus. The lips are defined by the orbicularis oris muscle, and the cheeks defined by the buccinator and masseter muscles (7), all of which work together to contain the bolus during the oral preparatory and oral phase of swallowing. The roof of the mouth (hard palate) is defined by the maxilla and the palatine bone. Posteriorly, the soft palate and velum form a flexible and moveable barrier at the back of the mouth to prevent nasal regurgitation and keep food from spilling into the pharynx before an intended swallow. The tongue, a large group of muscles, sits within the oral cavity. The extrinsic muscles (the genioglossus, hyoglossus and styloglossus) of the tongue anchor at the mandible, hyoid bone, and styloid process of the cranium. The internal muscles of the tongue include the superior longitudinal muscle, the inferior longitudinal muscle, the vertical muscle, and the transverse muscles (7). These structures work together to position and shape the tongue in order to contain the bolus and prepare it for swallowing. Additionally, the tongue is primarily responsible for propulsion of the bolus into the proximal oesophagus.

Nasal Cavity

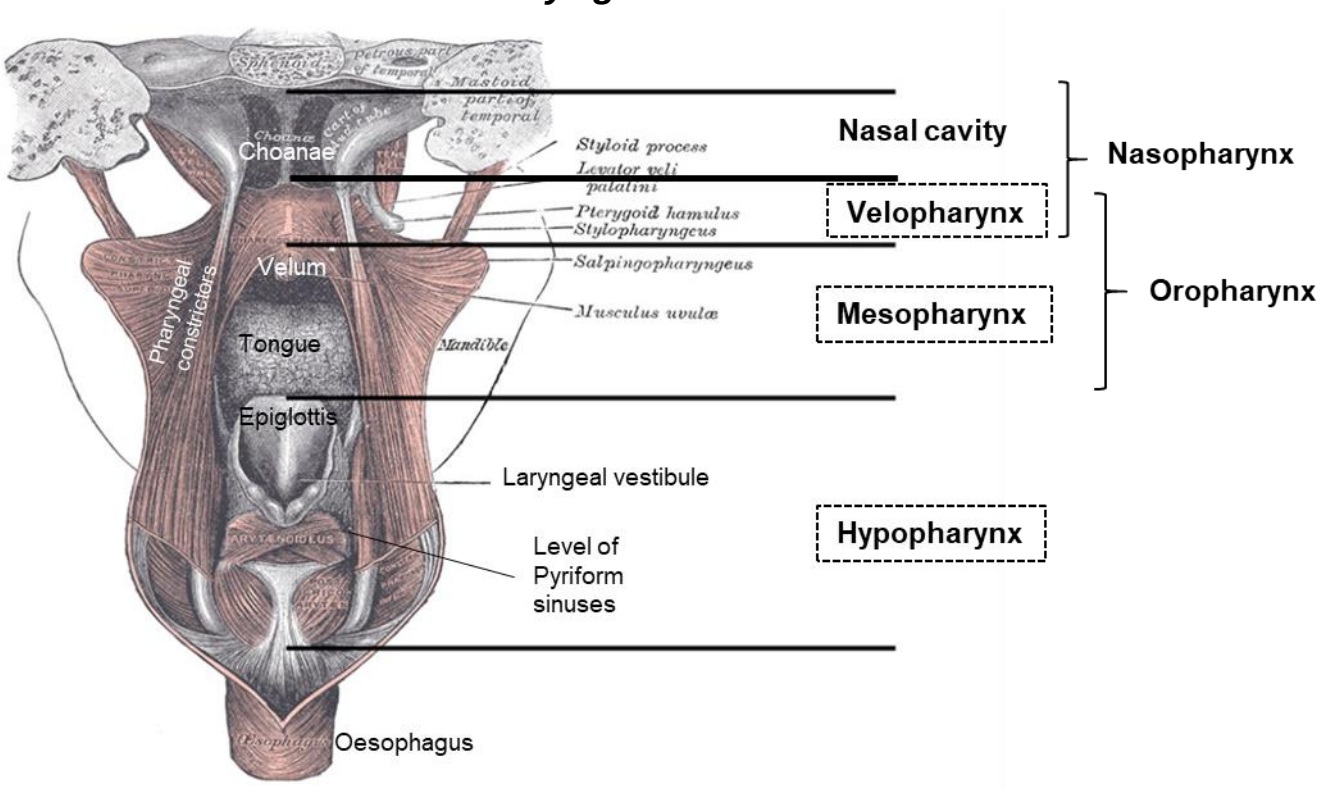
Another structure relevant to this thesis is the nasal cavity, which is divided into two parts by a medial cartilage. During respiration, air is drawn into two airway conduits, the

nostrils/nares/naris (7, 26). During the P-HRM-I procedure, a recording catheter is passed via either nostril, through the nasal cavity, choanae; see Figure 2, into the pharynx, past the UOS and into the oesophagus. Inferiorly, the maxilla palatine process provides a rigid boundary between the nasal and oral cavity. Tissue extending beyond this bony process forms the soft palate and velum (7). The nasal cavity humidifies, and filters air breathed into the pharynx, airway, and lungs (7, 26).

Pharynx

The pharynx is a channel for both airflow during respiration and bolus movement during swallowing (195). It comprises three overarching zones: the nasopharynx, oropharynx and hypopharynx; see Figure 2 (357). The P-HRM-I parameters reflect the contractility of the pharyngeal muscles within three sub-zones, the *velopharynx, mesopharynx and hypopharynx*. These are described in more detail below.

Figure 2. *The Anatomical Structures Comprised in Each Pharyngeal Zone*



Note. This figure illustrates the anatomical structures of the three pharyngeal zones: velopharynx, mesopharynx and hypopharynx. This image originates from *Gray H, Anatomy of the human body 1918, Philadelphia: Lea & Fibiger, in the public domain*. Minor amendments have been made to this image to demarcate regions of interest and improve text clarity.

Velopharynx

The space where the velum meets the pharynx is known as the velopharynx. The superior pharyngeal constrictors; see Figure 2, define the posterior pharyngeal wall of this region and activate during the pharyngeal stripping wave to seal the nasal cavity and clear the bolus. During swallowing investigations, P-HRM-I parameters measure velopharyngeal contractility. The palatopharyngeus, salpingopharyngeus, and stylopharyngeus muscles run laterally from the border of the hard palate and styloid process respectively, to the thyroid cartilage of the larynx, working together to lift the pharynx and seal the velopharynx during swallowing. The velopharynx acts as a passage for airflow, a drainage area for secretions from the nose,

paranasal sinuses and eustachian tubes into the pharynx to be cleared by swallowing; and it also acts as a resonator for speech production (26). The adenoids are positioned at the top of the velopharynx. The velum demarcates the anterior boundary of the velopharynx and during the act of swallowing the soft palate and velum elevate to prevent nasal regurgitation (26).

Mesopharynx

As a segment of the oropharynx, the posterior extension of the oral cavity is referred to as the mesopharynx. It is the space behind the anterior faucial arches extending posteriorly to the pharyngeal wall and inferiorly to the base of tongue and top part of the epiglottis; see Figure 2. Therefore, during P-HRM-I investigation, the mesopharyngeal pressure measured likely represents tongue base retraction. The pharyngeal constrictor muscles (medial and inferior constrictors) form the posterior pharyngeal wall of this region. Within the mesopharynx, the palatine tonsils sit between the anterior and posterior faucial arches.

Hypopharynx

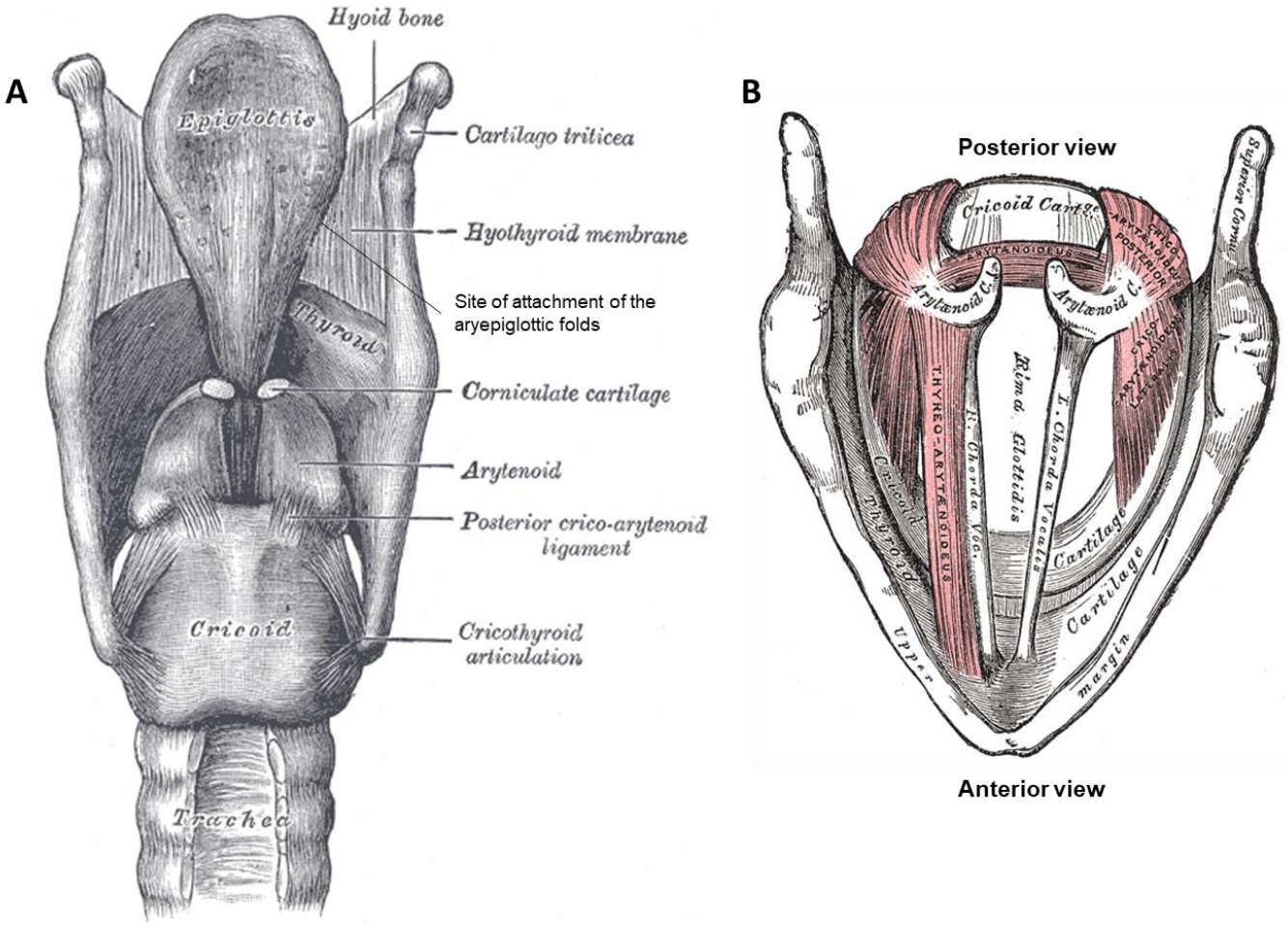
The hypopharynx is demarcated from the tip of the epiglottis down to the cricopharyngeus muscle of the UOS; see Figure 2. During P-HRM-I examinations, hypopharyngeal contractility and distension during bolus flow can be calculated. The inferior pharyngeal constrictor muscles form the posterior wall and attach to the thyroid cartilage of the larynx (26). The space between the posterior pharyngeal wall and the thyroid cartilage forms two lateral pyriform sinuses (left and right), which sit at the level of the cricopharyngeus muscle.

Larynx

The larynx is an intricate structure comprising various cartilages, muscles, and ligaments. The larynx forms the top of the airway, above the trachea; see Figure 3. The larynx is structured by the cricoid and thyroid cartilages; and on the posterior surface of the thyroid cartilage the epiglottis is anchored but is positioned anteriorly in the larynx overall; see panel A in Figure 35.

Within the cricoid cartilage, the paired arytenoid cartilages sit posteriorly, and the true vocal folds extend anteriorly to meet the thyroid cartilage; see panel B in Figure 3. In infants the epiglottis is narrow and angled away from the trachea to allow for closer proximity with the velum during sucking (358). The epiglottis is instrumental in protecting the airway during swallowing and deflects posteriorly during pharyngeal swallowing to seal the airway. The aryepiglottic (or false vocal) folds attach laterally, indicated in Figure 3, and sit above the true vocal folds in the laryngeal entrance. As seen above in Figure 1, the infant larynx is positioned directly under the base of tongue; therefore, the oropharynx in this age group is limited to the velopharynx only (26, 314), as the velopharynx meets the hypopharynx. However, by four years of age the larynx has descended from the base of tongue to form the mesopharyngeal zone within the oropharynx.

Figure 3. *Anatomy of the Larynx*



Note. This figure demonstrates laryngeal anatomy. Both images originate from *Lewis, Anatomy of the Human Body, 1918, currently in the public domain*. Minor amendments have been made to include labels.

Oesophagus

The oesophagus is a luminal muscular structure connecting the pharynx to the stomach and sits posteriorly to the airway (23). An infant's oesophagus is approximately 11cm long (29) whereas an adult's oesophagus varies from 21-27cm in length (2). The proximal oesophagus is comprised of striated muscle fibres which respond to central neural control. The remaining body of the oesophagus is comprised of smooth muscle fibres, which are controlled by the enteric nervous system. The upper oesophageal sphincter (UOS) demarcates the upper part

of the oesophagus, acting to prevent the entry of air into the gastric system. The lower oesophageal sphincter (LOS) demarcates the lowest segment of the oesophagus and acts to prevent the movement of gastric content into the oesophagus and airway.

Upper and Lower Oesophageal Sphincters

The UOS sits between the distal pharynx and proximal oesophagus (24) and is a high-pressure zone at rest. The cricopharyngeus muscle is predominantly responsible for forming this high-pressure zone, strapping around the top of the oesophagus, and attaching laterally to the cricoid cartilage in a C shape (1, 24). Other muscles of the UOS zone include the thyropharyngeus and cervical oesophageal muscle. The cricopharyngeus muscle is in a tonically contracted state at rest to prevent ingestion of air during respiration (aerophagia), and the upward flow of gastric contents during and after swallowing (25). The cooperation of the UOS zone is instrumental to safe and effective swallowing, and its opening relies on efficient lingual propulsive forces, laryngeal elevation extent, and cricopharyngeal (CP) muscle relaxation (225).

Below the UOS, the oesophagus extends down as a muscular tube, through a foramen in the diaphragm to meet the stomach. The lower oesophageal sphincter (LOS) is a segment of oesophageal and diaphragmatic muscle which also creates a region of high intraluminal pressure at rest. It relaxes during oesophageal peristalsis (10) to allow passage of food and drink into the stomach.

Recognising the full continuum of the swallowing mechanism is critical when assessing swallowing physiology and pathophysiology as the functional relationships between the pharynx, larynx and oesophagus are interconnected and influence bolus movements in an antegrade direction from pharynx to oesophagus, as well as a retrograde direction from oesophagus to pharynx/larynx (359).

Overview of the Typical Development of Swallowing Physiology in Children

The maturation of swallowing coordination required to sustain nutritive sucking is established between 33-36 weeks gestation (26, 360, 361), although the neurodevelopment of swallowing function is the first motor response to develop, and is thought to begin in utero as early as 11-13 weeks gestation (26, 362). Rhythmical motor patterns drive the suckling action in infants, a reflex that is controlled by central pattern generators (CPGs) in the brain stem (25, 26, 363). The breathing pattern and coordination of nutritive swallowing during sucking called the suck-swallow-breathe cycle demonstrates the intricate coordination of the aerodigestive mechanism (7, 26). An effective lip seal, together with pronounced back and forth drawing tongue movements, together with opening and closure from the jaw, ensures infants can draw milk into their mouth (7). Several laryngeal chemo-reflexes and airway protective mechanisms are in place in newborn infants and are initiated when strongly acidic or heavily alkaline solutions enter the airway. These reflexes include startle, rapid swallowing, apnoea, laryngeal constriction, hypertension, and bradycardia (364). The airway protective mechanism changes as an infant matures and the probability of a cough response increases with infant age, while the probability of rapid swallowing and apnoea reduces with age (364). Airway protection also occurs with a pattern of post-swallow expiration to guard against aspiration. A mid-expiratory swallowing pattern, where the infant begins expiration, swallows and then continues the remainder of the expiratory breath, has been observed in infants shortly after birth (365). The suck-swallow-breathe cycle shifts to an inspiration, swallow, and expiration pattern from approximately 6 months of age (365, 366). Maturation of neurological and anatomical swallowing and airway structures most likely accounts for this change, whereby reflexive swallowing evolves to a more volitional process with experiential learning (314). The peripheral nervous system continues to mature over the first 2 years of life as new feeding experiences stimulate development of learning required for new textures (367).

At 6 months, lingual movements during sucking adapt from a front-to-back to an up-and-down lingual action, with strong activity of the intrinsic tongue muscles. Smaller vertical jaw movements are needed by this age, but a firmer lip seal is essential to maintain negative pressure in the mouth in order to draw liquid while drinking (7, 26). Coinciding with these physiological sucking skill changes, typically developing infants aged 4-7 months transition to pureed foods, such as rice cereal. Further anatomical developments occur with resorption of sucking pads, the increase in size of the pharyngeal chamber, reduced overlap of the soft palate and epiglottis, growth of an infant's mandible and the emergence of dentition allowing for oral preparation of more solid textures (26, 357, 368). Lip tone develops to control and contain more textured food types, and tongue lateralization enables more proficient bolus preparation (7, 26). Infants and young children rely on their parents/carers to provide the appropriate textures and range of consistencies necessary for healthy progression of feeding skills. As increased textured foods are offered, the sensory and tactile systems are stimulated (364). Additionally, jaw strength, lip control and the range of lingual movements necessary to form a smooth, cohesive bolus for safe swallowing chewing skills develop (357, 364). It is not uncommon for normal developing infants to cough, gag, and spit food as they establish a tolerance of a range of textures (7, 26).

In a typically developing infant, there is usually an easy transition from sucking from a nipple to drinking from a cup. The process can be introduced around 6 months of age; however, it may take several months before a child becomes a functional cup drinker. The transition relies on maturation of aerodigestive reflexes, changes in jaw stability, maturation of tongue and lip movements, and the development of eye-hand coordination (361, 369).

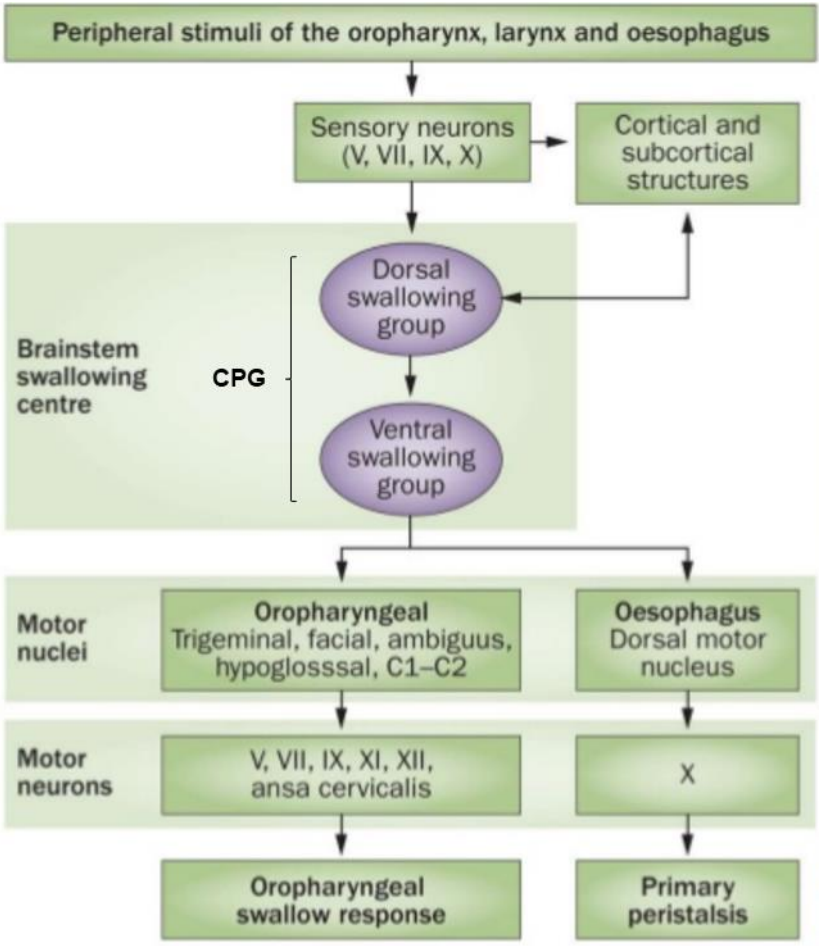
Neural Control of Oropharyngeal Swallowing

The swallowing response is one of the most intricate motor functions in humans as it requires coordination of 23 pairs of muscles in the mouth, pharynx, larynx and oesophagus (223). The swallowing process, from the oral to the oesophageal phase, is coordinated and controlled by the brainstem, cortical central pathways and the enteric nervous system (223, 363). There is an interconnected reflex mechanism between the pharynx, larynx, and oesophagus to protect the airway from foreign body (usually food and fluid) invasion and optimise bolus passage through the UOS and LOS. For example, in the event of reflux, these reflexes cause elevated UOS contraction to prevent retrograde return of the bolus from the oesophagus into the pharynx or larynx. Reflexes such as laryngo-UOS contractile reflex, and the oesophago-glottal closure reflex aim to prevent direct invasion to the airway (359). In newborns and very young infants, a range of stimulatory reflexes and respiratory patterns have been measured with a volumetric dose-response. Important work by Jadcherla and colleagues explores the intricate processes of infantile airway protection, including the pharyngo-glottal reflex during deglutition (219, 221, 332, 342, 370, 371).

The cerebral cortex controls the oral phase and the initiation of the pharyngeal phase of swallowing (223), but is less essential for the follow through of the pharyngeal and oesophageal stages (372). Within the medulla oblongata of the brainstem, CPGs have a principal function in the control of the pharyngeal motor action of swallowing, with interconnections from afferent and efferent impulses and inter-neuronal activity (223). The left and right sides of the brainstem have separate CPGs, which, within themselves are a complete neural circuit capable of triggering the swallowing response (223). Within the CPGs, the dorsal swallowing group receives sensory information via cranial nerves (V, VII, IX, and X), which innervate the swallowing structures. The ventral swallowing group is the main efferent motor hub, and there is output from the ventral swallowing group via cranial nerves (V, VII, IX, X, and XII) to the musculature required for swallowing function; see Figure 36 (223, 373). Additional to

swallowing, the CPGs share many of the same cranial motor fibres for the innervation of the cervical muscles needed for coughing and gagging (374), functions which are activated when the airway is invaded by stimulants such as food, fluid or chemical particles.

Figure 4. ***Neural Control of Swallowing***



Note. This figure demonstrates the neural control of the swallowing response. The brainstem central pattern generators (CPG) receive peripheral input via sensory neurons and the cortical and subcortical structures before a motor response is triggered to initiate the oropharyngeal swallow response. Primary peristalsis of the oesophagus is triggered by the dorsal motor nucleus. *This image originates from Nature Reviews Gastroenterology & Hepatology reproduced with permission.*

As has also been detailed in section 2.3.1 in the literature review of this thesis, the initiation of a swallow causes a ‘leading complex’ of neuroregulation which occurs in anticipation of bolus propulsion: soft palate elevation creates velopharyngeal pressures to seal the nasal cavity,

hyolaryngeal elevation commences, and cricopharyngeus muscle relaxation begins, all to prepare the pharyngeal chamber for bolus passage (195). Lingual propulsion of the bolus occurs, and pharyngeal and UOS distension (extent and duration) are modulated (224) to accommodate bolus characteristics, such as size, consistency and temperature. Epiglottic deflection and vocal fold adduction protect the airway, and the pharyngeal stripping wave follows lingual propulsion as a bolus clearing force (24). Once the bolus has travelled through the pharynx, laryngeal closure ceases, the pharynx returns to its resting position for respiration and the UOS resumes its tonic resting state as a high-pressure zone between the pharynx and oesophagus (24).

Oropharyngeal Dysphagia

Feeding disorders in children are defined according to the compromised oral intake relating to several factors: medical, dietary, skill based and/or impaired social wellbeing within the caregiver-child relationship (5). This recently published definition highlights the importance of the development between several anatomical and physiological systems, occurring alongside the developing relationship between caregiver and child (5). All components need to be considered for comprehensive assessment and management of swallowing and feeding disorders.

In children, neural maturation and appropriate sensory and motor development are vital for optimal deglutition, airway protection and nutrition (10). Oropharyngeal dysphagia occurs with specific disruption to the swallowing process caused by several potential factors: premature birth; anatomical malformations of the swallowing mechanism (such as tongue tie, cleft lip and/or palate, jaw position and size i.e., micrognathia/retrognathia/prognathia), laryngeal disorders (such as laryngeal cleft, and laryngomalacia), neuro-muscular conditions (such as cerebral palsy, or muscular dystrophy), developmental and congenital conditions (such as trisomy 21, velocardiofacial syndrome and 22q11 deletion syndrome), cardiopulmonary conditions (such as heart defects that lead to cyanosis), and gastrointestinal conditions (such as oesophageal atresia and gastroesophageal reflux). The swallowing response relies on neural control from the central and peripheral nervous system; therefore, when neuro-sensorimotor disorders exist, the degree of OPD depends on the extent of neurological deficit. Problems with the initiation of the swallow response may occur if the brainstem CPGs are affected. Damage or underdevelopment of the cranial nerves [(V) trigeminal, (VII) facial, (IX) glossopharyngeal, (X) vagus, (XI) accessory, and (XII) hypoglossal], may lead to muscle weakness, incoordination and/or sensory loss (2). Deficits with the function of any of the regions supplied by these nerves contribute to OPD. Overall, OPD leads to an inefficiency of bolus transfer from the oral cavity into the oesophagus, and the acute consequences relate to a

child's increased risk of airway invasion (i.e. penetration or aspiration of food, liquid or oral secretions) (8, 375).

Airway Invasion

Penetration is defined as the entry of swallow material or secretions into the laryngeal vestibule, without passing the vocal folds. Isolated laryngeal penetration occurs in the absence of aspiration (376). Aspiration is defined as the movement of food/ fluid/ secretions below the vocal folds into the trachea (68, 376). An 8-point penetration aspiration scale (see Table 1 below), developed by Rosenbek and colleagues (68) which classifies the degree of airway invasion seen on VFSS, is well established and widely used in both paediatric and adult studies.

Table 1. ***The Penetration Aspiration Scale***

Score	Classification	Description
1	None	No entry of material into the larynx or trachea
2	Penetration	Entry of material into the larynx with clearing
3	Penetration	Entry of material into the larynx without clearing
4	Penetration	Material contacts the true vocal folds with clearing
5	Penetration	Material contacts the true vocal folds without clearing the larynx
6	Aspiration	Material enters the trachea and is spontaneously cleared into the larynx or pharynx
7	Aspiration	Material enters the trachea and is not cleared following attempts
8	Aspiration	Material enters the trachea with no attempt to clear

Note. This table represents the well-established penetration aspiration scale (PAS) developed by: *Rosenbek JC, Robbins JA, Roecker EB, Coyle JL, Wood JL. A penetration-aspiration scale. Dysphagia. 1996;11(2):93-8.*

Penetration or aspiration may occur before, during or after the swallow depending on the physiological deficit causing OPD. Premature arrival of the bolus into the pharynx, failed laryngeal vestibule closure during the swallow, and post swallow residue are the main visual features of unsafe swallowing, all of which place a child at risk of penetration, aspiration or choking. The consequences of aspiration depend on an individual's ability to clear the airway and/or cope with aspirated materials by means of a strong and effective immune system. This pertains particularly to neurological status, intact cough reflex, throat clearing ability, mobility and ability to exert breathing as a part of daily activities (8, 12, 26, 34). The main adverse health outcomes of paediatric OPD relate to poor respiratory health (chest infections, progressive lung disease, bronchiectasis, chronic cough, recurrent wheeze, atelectasis, and aspiration pneumonia), malnutrition, dehydration, failure to thrive and in the worst cases, death (3, 5, 11, 12, 13). The quality of life of children with OPD and their families is also significantly impacted by these risks and stressors (14). The physiological features of OPD and its impact on health is further discussed in the Introduction and Literature review of this thesis.

Appendix 2

This appendix includes copies of the Dysphagia Disorders Survey (DDS) [removed due to copyright restriction], Functional Oral Intake Scale (FOIS) used in Chapter 8 and Modified Functional Oral Intake Scale (M FOIS) referred to in the Literature Review.

Functional Oral Intake Scale (FOIS)

Levels	FOIS Items
Level 1	Nothing by mouth
Level 2	Tube dependent with minimal attempts of food or liquid
Level 3	Tube dependent with consistent oral intake of food or liquid
Level 4	Total oral diet of a single consistency
Level 5	Total oral diet with multiple consistencies, but requiring special preparation or compensation
Level 6	Total oral diet with multiple consistencies without special preparation, but with specific food limitations
Level 7	Total oral diet with no restrictions

Note. This table was recreated from *Crary MA, Mann GDC, 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.*

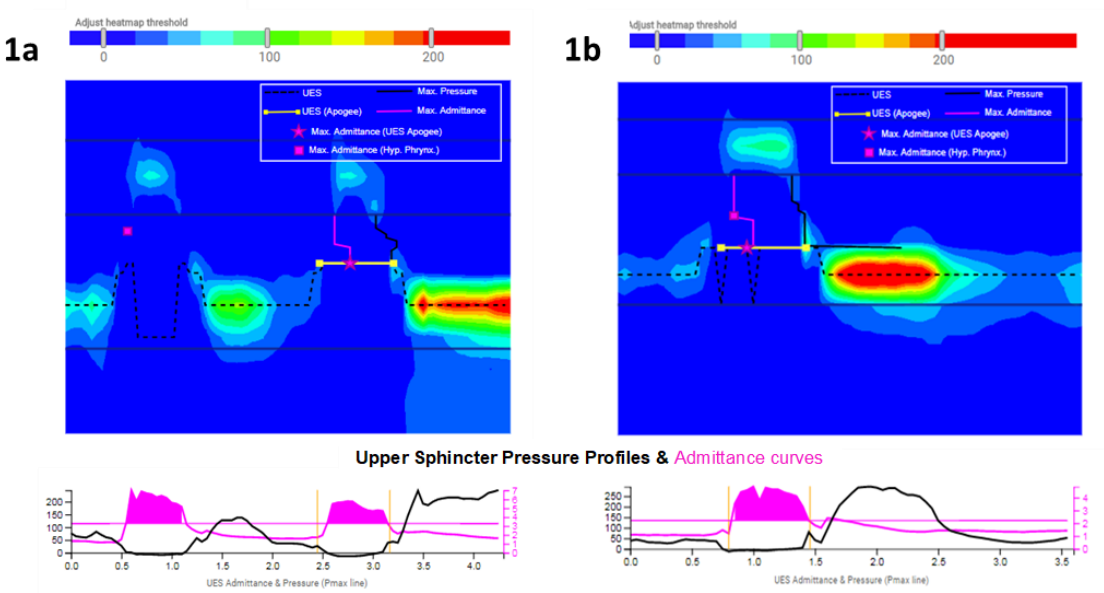
Modified Functional Oral Intake Scale (M FOIS)

Levels	FOIS Items
Level 1	Nothing by mouth
Level 2	Tube dependent with minimal attempts of food or liquid
Level 3	Tube dependent with consistent oral intake of food or liquid
Level 4-6	Expansion of oral diet not reached*
Level 7	Expansion of oral diet reached*

Note. This table was recreated based on *Coppens CH, van den Engel-Hoek L, Scharbatke H, de Groot SAF, Draaisma JMT. Dysphagia in children with repaired oesophageal atresia. Eur J Pediatr. 2016;175(9):1209-17*. *As the authors of this journal article state: 'Normal expansion of oral diet was considered reached when introduction of solid foods in pureed form started before 9 months of age and the introduction of mashed foods and soft lumps started before 12 months of age'.

Appendix 3

Patient Case Example: Piecemeal Deglutition with Thin Fluids - Weak Lingual Propulsion and Pharyngeal Vigour[15]



An ambulant 7-year-old boy with congenital muscular dystrophy, no chest health issues, however increased **coughing with thin fluids** (IDDSI level 0). *Functional oral intake score* of 6: tolerating a soft diet, no liquid modifications (311). *The Dysphagia Disorders Survey* (45) revealed **no overt signs of OPD** (i.e. cough, throat clearing), only occasional multiple swallowing. *Dysphagia Management Staging Scale* (45) showed **mild severity of dysphagia symptoms**. Qualitative assessment of pressure topography graphs shows significantly reduced pharyngeal strength for liquids and semisolids (1a IDDSI level 0 (thin) and 1b IDDSI level 4 (extremely thick)). Additionally, **piecemeal deglutition** with thin fluids is indicated and the pink admittance curves in Figure 1a show bolus in both swallows. Automated analysis using Swallow Gateway™ confirmed abnormally **low pharyngeal vigour** (*peak P* 19 mmHg), and **weak lingual propulsion** (*velopharyngeal–tongue base integral* 34 mmHg). **Adequate UOS open time** (0.68 sec), indicated by the vertical yellow lines in the Admittance Profile, and **adequate UOS relaxation pressures** (-7.97 mmHg) were evident to support safe deglutition of thin fluids and semisolids. With pacing and prompts to remain alert this child continued symptom free over the following 12-month period.

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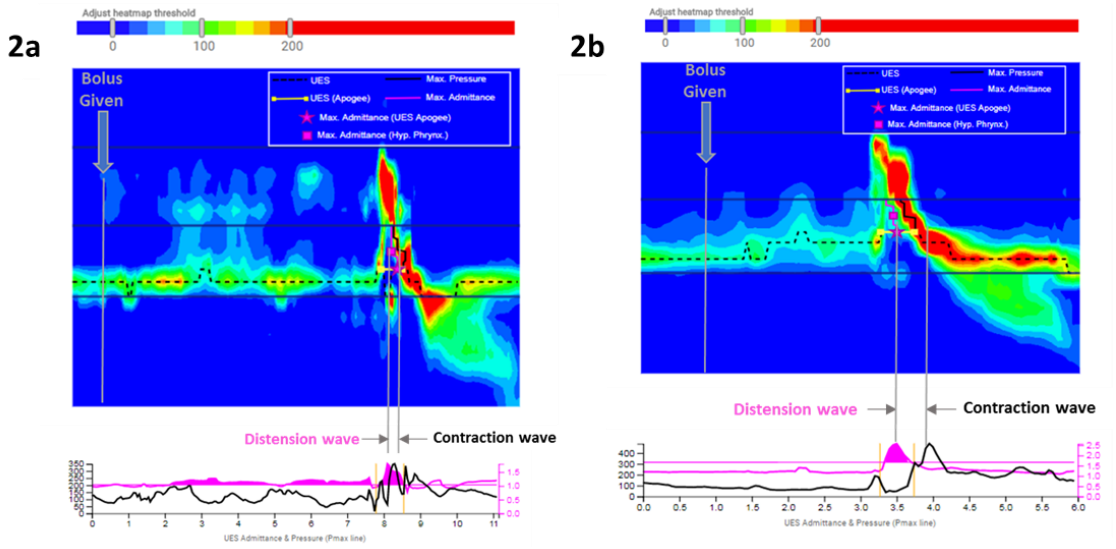
[15] The text in this appendix originates from an invited manuscript:

Ferris L, Omari T. Pharyngeal manometry in pediatric dysphagia assessment. Perspectives of the ASHA Special Interest Groups. 2019;4(4):656-82. Reference (21). Some wording changes have been made for inclusion in this thesis.

Appendix 4

Patient Case Example – Delayed Swallow Initiation, Elevated Hypopharyngeal Bolus Pressure in Relation to Uncoordinated Timing of Swallow Events[16]



Upper Sphincter Pressure Profiles & Admittance curves

Five-year-old boy, with spastic quadriplegic cerebral palsy and history of recurrent chest infections. **Silent aspiration** on thin (IDDSI 0) and mildly thickened fluids (IDDSI 2) on VFSS. *Functional Oral Intake Score* of 5: multiple consistencies require specific preparation (311) [IDDSI level 5 (minced & moist diet), and IDDSI level 3 (moderately thickened fluids)]. The *Dysphagia Disorders Survey* (Sheppard et al., 2014) revealed **overt signs of OPD** (i.e. cough, throat clearing, multiple swallowing), and an overall *Dysphagia Management Staging Scale* (Sheppard et al., 2014) was **severe rating of dysphagia symptoms**. Qualitative assessment of pressure topography graph in Figure 2a shows **delayed swallow initiation** after the 2ml liquid bolus was placed in the mouth (see bolus given), slightly improved with 3ml viscous bolus in Figure 2b. Automated analysis using Swallow Gateway™ revealed i) a**bnormal bolus presence time** due to premature spillage for liquids, shown by pink admittance readings prior to the swallow, see 3a (BPT of 3.6 sec), ii) **significantly elevated hypopharyngeal intra-bolus pressure** (*hP IBP* 59 mmHg for liquids, and 102 mmHg for viscous swallows). iii) abnormal time from pharyngeal distension (indicated by the peak of the pink admittance curve) to the pharyngeal contraction (indicated by the peak of the black pressure curve. This is known as the *Distension – Contraction Latency* 0.16 sec for 3a, and 0.13 sec for 3b, suggesting an **inability to propel the bolus ahead of the pharyngeal stripping wave,** and iv) adequate **UOS relaxation pressures** for mis-timed bolus flow (UOS IRP 5.6 mmHg liquids, 3.8 mmHg viscous). A combination of premature spillage and poor coordination of lingual propulsion are the likely causes for this child's swallow profile.

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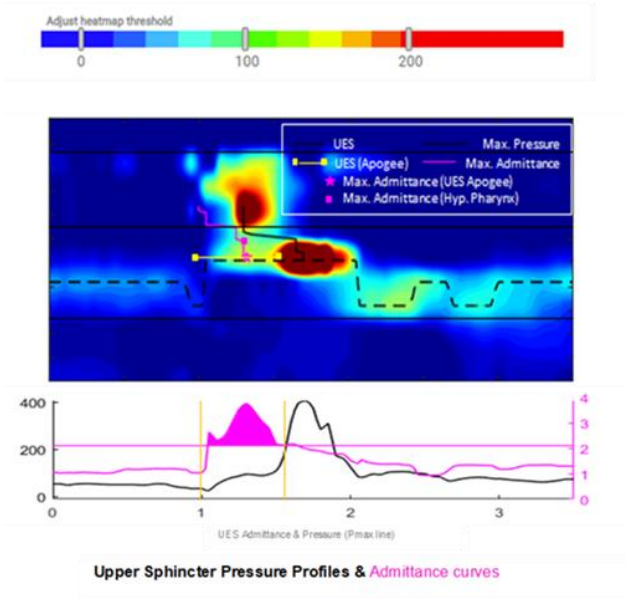
[16] The text in this appendix originates from an invited manuscript:

Ferris L, Omari T. Pharyngeal manometry in pediatric dysphagia assessment. Perspectives of the ASHA Special Interest Groups. 2019;4(4):656-82. Reference (21). Some wording changes have been made for inclusion in this thesis.

Appendix 5

Patient Case Example – UOS Obstruction for Investigation of Cricopharyngeal Achalasia[17]



Five-month-old boy with a history of feeding difficulties since birth. VFSS showed a normal oral phase, but severely impaired pharyngeal phase, with **silent aspiration** on all consistencies trialled [IDDSI level 0 (thin), 1 (slightly), 2 (mildly) and 3 (moderately thickened) consistencies]. *Functional Oral Intake Score* of 1: **receiving full nasogastric feeds**. The *Dysphagia Disorders Survey* was not age appropriate, however clinical reports indicated **severe rating of dysphagia symptoms**. Qualitative evaluation of pressure topography graphs shows adequate pharyngeal vigour, but significantly elevated hypopharyngeal pressures; see Figure 4. Automated analysis confirmed i) **abnormally high hypopharyngeal intra-bolus pressures** (*hP IBP* 88 mmHg), and ii) **significantly elevated UOS relaxation pressures** (*UOS IRP* 28 mmHg). These findings are consistent with a diagnosis of UOS obstruction. This child successfully received **cricopharyngeal muscle botox therapy**, which remediated aspiration, nasal regurgitation, and post swallow residue, as seen on VFSS.

[17] The text in this appendix originates from an invited manuscript: Ferris L, Omari T. Pharyngeal manometry in pediatric dysphagia assessment. ASHA SIG. 2019;4(4):656-82. Reference (21). Some wording changes have been made for inclusion in this thesis.

Appendix 6 - The Main Paediatric Manometry Studies since 1998[18]

Study	Cohort details	Manometry type	Bolus Type	Parameters measured	Main findings
Characterization of Esophageal Body and Lower Esophageal Sphincter Motor Function in the Very Premature Neonate (377)					
Omari et al, 1999	n=12 Neonates MA 30 weeks	2 x 2 mm micro manometric sleeve assemblies (length varied for neonate PMA and weight)	Regular nasogastric bolus feed	-Oesophageal pressure wave sequences: Synchronous Retrograde Incomplete -LOS pressure -LOS relaxation +nadir -TLOSR -GOR episodes (oesophageal & intra-gastric equalization)	This study indicated that oesophageal function is fully developed by 26 weeks gestation. LOS tone is sufficient to maintain esophago-gastric competence and pharyngeal swallows are well coordinated to initiate oesophageal contraction and appropriate LOS relaxation. Transient LOS relaxation is well developed by 26 weeks and is likely the predominant mechanism of reflux.
Oroesophageal Motor Disorders in Pierre Robin Syndrome (378)					
Baujat et al, 2001	n=35 Pierre Robin Sequence MA 4.8 weeks	Continuous water perfused oesophageal manometry	Dry swallows only		Authors propose a potential lack of sensitivity of the manometry technique employed or underlying physiological parameters which may have influenced sucking ability. 50% of the cohort experienced LOS hypertonia and oesophageal dyskinesia, despite a presentation of GOR symptoms which usually correlate with LOS hypotonia.

Motor Dysfunction of the Upper Digestive Tract in Pierre Robin Sequence as Assessed by Sucking- Swallowing Electromyography and Esophageal Manometry (379)					
Baudon et al, 2002	n=28 Pierre Robin Sequence Age 15-45 days	Conventional water perfused manometry with 3 pressure-sensor transducers (Medtronic, France) + Monopolar needle-electrode EMG (genioglossus and thyrohyoid muscles)	Sugar water from bottle	-LOS resting pressure -Oesophageal peristalsis 10 swallows: -wave amplitude (abnormal >150mmHg) -propagation (abnormal if multi-peaked or >7 sec duration, or retrograde) -morphologic features -LOS relaxation -UOS resting pressure -UOS relaxation during swallows	EMG and oesophageal manometry can reveal dysfunction of the motor organisation of the tongue, pharynx, and oesophagus. A high frequency of sucking disorders with concomitant peristalsis and abnormal sphincter pressures and relaxation were found using both techniques.
Videomanometry Reveals Clinically Relevant Parameters of Swallowing in Children (170)					
Rommel et al, 2006	n=8 (6F) Broad dysphagia (Neurological, genetic, gastrointestinal	Two catheter protocol: 1.6 mm Solid state catheter, 3 pressure sensors	Ad libitum milk + Lomeron (contrast material) boluses by bottle or spoon	-Oropharyngeal transit time -Pharyngeal contraction duration -UOS relaxation duration -UOS relaxation from onset to max -UOS relaxation interval corresponding to opening -Epiglottic movement	The first objective videomanometric oropharyngeal, pharyngeal, and UOS results presented in paediatrics. It is concluded that videomanometric techniques can be performed in children and may provide new insights into the pathophysiology of feeding difficulties. Further studies are required to develop precise diagnostic criteria.

[18] Study titles are presented in the highlighted row with spelling as shown in publication. References relating to bibliography are shown in brackets. Studies are displayed in chronological order.

	medical background) MA=18 mo	2 mm air perfused Dent-sleeve catheter (infants) 2.0 mm air perfused manometry assembly with Dentsleeve parafilmed together (3.6mm in total) + VFSS		-Pharyngeal shortening -Movements of pharyngeal wall AP -UOS opening -Tongue driving force -Amplitude pharyngeal contraction -Resting UOS pressure -UOS relaxation -Area of UOS relaxation	
Pharyngeal Swallowing: Defining Pharyngeal and Upper Esophageal Sphincter Relationships in Human Neonates (370)					
Jadcherla et al, 2007	n=10 Healthy neonates PMA 39 weeks	Micromanometry catheter (Pharyngeal port, Dentsleeve, 3 x esophageal ports) + submental EMG	Air (0.1-2ml) Sterile water (0.1 – 0.5ml) at least 2 of each volume	-Pharyngeal reflexive swallows (PRS) within 5 seconds of pharyngeal provocation - Pharyngo-UOS-contractile reflex (PUCR) > 4 mmHg within UOS after provocation -Manometric waveforms -UOS relaxation -UOS contraction -UOS basal pressure	PRS was more frequent than PUCR, and responses were greater for water compared to air provocation. These reflexes are proposed for use in FEES. These reflexes can indicate a defect in the neurocircuitry for normal swallowing in infants, and these data serve as a reference for future studies.
Development of Esophageal Peristalsis in Preterm and Term Neonates (380)					

Staiano et al, 2007	n=16 Neonates PMA 32 weeks Term MA 38 weeks	2.25 mm High resolution water perfused catheter with Dentsleeve +Submental EMG to determine pharyngeal swallows	0.25 – 0.5ml room temp boluses 5% sucrose solution	-Presence of the major pressure segments and intersegmental troughs as depicted topographically, graded: Absent Present in < 50 % Present in > 50 % Present in > 80 %	The second pressure segment in the mid oesophagus is well established before term. Other peristaltic segments continue to develop towards term but are still incomplete in almost half the swallows analysed. These findings contribute to a better understanding of infant reflux disease.
Segmental Characteristics of Oesophageal Peristalsis in Paediatric Patients (381)					
Staiano et al, 2008	n=40 Neonates <1 mo old Infants/toddlers 1 mo – 2yr) Children (2-14yr) MA 7.3 yrs	2.25 mm High resolution water perfused catheter with Dentsleeve	Water boluses 0.5 – 4ml depending on subject age x at least 10 swallows captured	-MMS for topographic analysis -Pressure segments as described above. -LOS relaxation	HRM is clinically useful across the paediatric age spectrum studied. The distinctive pressure sequences observed in adults were characterised in this cohort of neonates to children. The segmental character of oesophageal peristalsis should be considered in all manometric investigations, e.g. when testing pharmacological responses and clearance mechanisms.
Videomanometric Evaluation of Pharyngo-Oesophageal Dysmotility in Children with Velocardiofacial Syndrome (245)					
Rommel et al, 2008	n=3 case series	12 channel High resolution manometry +	Case 1: 1 x trial liquid	-UOS relaxation values -UOS relaxation duration	High resolution videomanometry (HRVM) enabled subtle distinction between pathophysiology and characterization of pharyngeal and UOS dysfunction in children with

	Velocardiofacial syndrome 2yr old F 1½ yr old F 3 yr old M	Simultaneous VFSS	1 x trial semisolid Case 2: Thin fluid, thickened, and semisolid Case 3: Dry, wet and solid foods	-UOS amplitudes which indicated spasm -UOS spasm duration -Direction of pharyngeal pressure waves (antegrade, synchronous, retrograde) -pharyngeal pressure sequence coordination was commented on -pharyngeal peak amplitudes Videofluoroscopy to detect bolus flow, evidence of aspiration, residue, pooling, and anatomical structures and movements	VCFS, which assisted in tailored interventions for these 3 children: UOS dilatation, UOS botox therapy, and nil orally until further development and readiness for oral intake. HRVM demonstrated that UOS dysfunction contributes to nasal regurgitation beyond failed palatal insufficiency in children with VCFS.
Evaluation and Management of Neonatal Dysphagia: Impact of Pharyngoesophageal Motility Studies and Multidisciplinary Feeding Strategy (302)					
Jadcherla et al, 2009	n=20 Neonates (medically heterogenous) MA 30 weeks	Micromanometry system with respiratory inductance plethysmography and monitoring of vital signs + submental EMG Previous VFSS recordings	Trial of bottle feeding	-Propagation of swallows -Peristaltic response to wet swallows (distribution of primary peristalsis) -Presence of suck-swallow rhythm during oral feeding challenge -Swallow frequency -Peristaltic velocity -Resting UOS and LOS pressures	This study identified the presence or absence of aero digestive reflexes between successful (defined based on ability to fully nipple feed upon discharge from hospital) and failing oral feeders, to guide the development of multidisciplinary feeding approaches for neonates. Manometric findings but not VFSS measures were statistically different between the feeding success group and failed groups.
Definition and Implications of Novel Pharyngo-Glottal Reflex in Human Infants using Concurrent Manometry Ultrasonography (130)					

Jadcherla et al, 2009	n=12 (8M) MA 27 weeks Neonates Healthy and orally fed at the time of study	Pharyngo-oesophageal water perfused manometry catheter with Dentsleeve + Ultrasound	Sterile water 0.1-, 0.3- and 0.5ml volumes	-Pharyngeal reflexive swallows -Response latency from glottal adduction -Response latency from provocation for pharyngeal reflexive swallows	The first reports of pharyngo-glottal closure reflex (PGCR) studied at 44 weeks post menstrual age in human infants. Spontaneous glottal closure during provoked swallowing is longer than natural swallowing. The adduction of the vocal folds occurred anywhere within the breath cycle. Reportedly a safe combined method (manometry and ultrasound) as an alternative to VFSS. Swallow pressures were not reported.
Pharyngeal Swallow Adaptations to Bolus Volume Measured with High-Resolution Manometry (151)					
Hoffman et al, 2010	n=226 MA 6.7yrs GERD patients (with and without structural abnormality)	4.5 mm water perfused manometry catheter with Dentsleeve + Previous pH monitoring, Barium and Endoscopy studies	1-5ml water boluses at each step (pull through technique) 10 wet swallows at LOS level	-LOS pressure -LOS relaxation -Peristaltic velocity (proximal & distal) -Peristaltic amplitude (proximal, mid & distal) -Duration of proximal contraction -Duration of mid and distal contractions (secondary)	LOS pressure and oesophageal velocity decrease with increasing age. Severely abnormal manometric findings were found for patients with oesophageal atresia or neuro-motor dysfunction. No specific motility abnormalities were related to presence of esophagitis or GOR on pH monitoring. Further studies are needed to better understand the interaction of GORD and manometric findings
Pediatric Esophageal High-Resolution Manometry: Utility of a Standardized Protocol and Size-Adjusted Pressure Topography Parameters (382)					
Goldani et al, 2010	n=30 Median age 10 yrs	3.8 mm high resolution water perfused catheters with e=sleeves	10 x 0.5 – 5ml water (age dependent)	-Basal LOS pressure -LOS inhibition -Automated MMS software measurements:	The first oesophageal HRM non-neonate paediatric study. Automated oesophageal measures are presented with an adjusted distal contractile integral (DCIa). A proposed paediatric protocol is presented:

		14 oesophageal pressure channels	*2 x infant <12 mo were given 0.5ml due to OPD, 100ml multiple rapid swallows (only in older children) Solid intake 2x3 cm (toast or other)	-Deglutitive EGJ relaxation -Pressurization front velocity -Distal contractile integral(adjusted) -Oesophageal body length	- No sedation - 3-minute settling period prior to swallow acquisition - 10 wet swallows 0.5 – 5ml - Multiple rapid swallowing (100mls) to investigate LOS inhibition to differentiate ineffective oesophageal motility from true achalasia.
Development of Pharyngo-Esophageal Physiology During Swallowing in the Preterm Infant (145)					
Rommel et al, 2011	n=18 Preterm infants Longitudinal study Age at 1st visit: 31-32 weeks 2nd visit: 33-34 weeks 3rd visit: 35-36 weeks	2.0 mm Custom designed water perfused manometry with Dentsleeve	30-minute settling time Breast or bottle feed Nutritive sucking bursts	-Mean pharyngeal peak pressure -Pharyngeal propagation velocity -UOS pressure at onset -UOS nadir pressure -Segmental pharyngeal peak pressure -UOS relaxation response time -Time between proximal peak amplitude – UOS nadir (coordination) -Time from distal pharyngeal peak amplitude and UOS nadir (effectiveness of clearance)	The first reports of developmental changes using segmental analysis of HRM recordings revealed subtle developmental differences in timing of pressure events in infant pharyngeal and UOS physiology. Amongst these differences were: - Reduced pharyngeal peak pressure 1 cm above the UOS pressure zone was seen in infants 31-32 weeks and disappeared with increasing age. This may be associated with bolus residue and possible aspiration. - Secondly UOS relaxation, nadir pressures and duration of UOS relaxation remain similar from 31 weeks onwards.

				*Each parameter calculated at 5 different pharyngeal levels (segmental analysis)	
Heterogeneity of Lower Esophageal Sphincter Function in Children with Achalasia (383)					
Morera et al, 2012	n=29 achalasia patients 16 controls All below 18yrs	Continuous perfused manometry with 4 port catheter	10x 3-5ml water at LOS level Pull through technique with further swallows in upper oesophagus if required	-LOS basal pressure -LOS relaxation Absent Present Abnormal % Normal % -LOS residual pressure Normal % Abnormal %	LOS dysfunction in children with achalasia is heterogeneous in 27 – 34 % (depending on the abnormal LOS parameter), although is abnormal most of the time in all patients. Partial relaxation is common in children with achalasia and partial relaxations, and some normal relaxations may occur. Perhaps sphincter function varies with time and may appear normal in early stages of the disease.
Characterization of Esophageal Motility Following Esophageal Atresia Repair using High-Resolution Esophageal Manometry (384)					
Lemoine et al, 2013	n=45 (25M) Median age 8 yrs Type C Oesophageal Atresia	2 solid state catheter protocol High resolution manometry 12 pressure sensors -2.75 mm -4.2 mm	10 x Water boluses 2ml < 5yrs 5ml > 5yrs	-UOS residual pressure -LOS basal pressure -LOS Integrated Relaxation Pressure -Distal contractile Integral/a -Contractile Front Velocity	Albeit retrospective in nature, this was the first HRM paediatric study of oesophageal atresia. No participants demonstrated normal peristalsis. 38% presented aperistalsis, 15% demonstrated pressurization pattern, and 47% with a distal oesophageal contraction. Automated oesophageal metrics were presented. Findings improve our understanding and allow precise characterisation of oesophageal dysmotility post OA repair. Further studies are needed.

		n=21 Previous endoscopy n=13 pH probe			
Physiology of Esophageal Sensorimotor Malfunctions in Neonatal Neurological Illness (332)					
Jadcherla et al, 2013	n=20 (6M) PMA 42 weeks Neurologically impaired neonates n=10 healthy control infants	Micromanometry water perfused system with multimodal provocation technique	15-minute accommodation period Air Water Apple juice Provocation to mid oesophagus	-Oesophago-deglutition response (ODR) -Secondary peristalsis -UOS resting pressure -Response latency to stimulus -Max UOS contraction -UOS contractile magnitude -UOS contractile reflex duration -LOS resting pressure	To test the effects of mechanosensitive, osmosensitive and chemosensitive stimulation with air, water and apple juice to the mid oesophagus. Oesophageal provocation responses to air, water and apple juice, were volume dependent and preserved in the neonatal group, showing exaggerated excitatory efferents with greater UOS and LOS pressure measures and longer relaxation compared to the control group. It is reported that pharyngeal swallows in the neonate group were dysfunctional due to the infrequent pharyngeal response to oesophageal provocation, likely due to impaired descending modulation from the brainstem and vagal nuclei.
Respiratory Events in Infants Presenting with Apparent Life-Threatening Events: is there an Explanation from Esophageal Motility? (223)					
Hasenstab et al, 2014	n=10	Micromanometry water perfused system +	No boluses offered	-Basal UOS pressure -Sphincteric response during ‘spontaneous respiratory event’	A study of respiratory events and oesophageal manometry in infants with ALTE. Deglutition is the most frequent oesophageal event related to ‘spontaneous

	infants from neonatal and infant feeding program with apparent life-threatening events (ALTE) (age not specified) n=10 healthy controls (age not specified)	Dentsleeves for UOS and LOS 5 ports through pharynx, proximal, middle, distal, stomach		Contraction Relaxation None -Post deglutitive UOS pressure -LOS basal pressure -Sphincteric response during 'spontaneous respiratory event' Contraction Relaxation None -LOS deglutitive nadir relaxation -Polymorphic oesophageal waveforms Multipeaks Prox/Mid/Distal -During SRE peristaltic characteristics -GOR events (TLOSR)	respiratory events', not GOR. The authors propose that swallow dependent SREs were deglutitive apnoea masquerading as central apnoea. They suggest brainstem dysregulation of superior, laryngeal, vagal, glossopharyngeal, superior pharyngeal and recurrent laryngeal nerve control. Prolonged respiratory inhibition in ALTE is possibly guided by primary peristalsis and ineffective oesophageal clearance. Speculated aerodigestive hypersensitity may be to blame in ALTE. Children with history of ALTE had significantly lower UOS basal pressures during SRE than controls, and postdeglutitive rise in UOS pressure occurred more frequently. These findings depict deficits in the central pattern generation of aerodigestive rhythms and regulations. Further work needed to define sensory-motor aspects of these aerodigestive reflexes.
Objective Assessment of Swallow Function in Children with Suspected Aspiration using Pharyngeal Automated Impedance Manometry (185)					
Rommel et al, 2014	n=20 MA 6 yrs Aspiration risk (Neurological,	2.5 mm solid-state high-resolution impedance manometry +	1 – 10ml liquid, semisolid and solid boluses (dependent on age and	-Pharyngeal peak pressure -Pharyngeal nadir impedance -Pressure and Nadir impedance -Time from nadir impedance to peak pressure	Pressure only metrics in the UOS were not altered in the presence of aspiration, however pressure at nadir impedance and the impedance-based pressure indicators were able to detect subtle change in the UOS response to bolus flow in the case of aspiration. Identification of subtle

	oesophageal dysmotility, GOR, congenital abnormality, ENT pathology)	Simultaneous VFSS	tolerance) given via syringe Only liquid used for analysis.	-Flow interval (impedance versus cumulative time) -UOS relaxation interval (UOS RI) -UOS nadir relaxation pressure -UOS nadir impedance (opening diameter) -UOS intra-bolus pressure (UOS IBP) -UOS resistance (UOS IBP/UOS RI) -Swallow Risk Index -Postswallow Residue score (impedance ratio)	differences in UOS function may be clinically valuable pre and post interventions for aspiration risk, e.g. UOS myotomy, and botox injection. The composite swallow risk index differentiated aspiration from non-aspiration cases, highlighting the potential utility of this tool in paediatric patients.
Applying the Chicago Classification Criteria of Esophageal Motility to a Pediatric Cohort: Effects of Patient Age and Size (319)					
Singendonk et al, 2014	N=76 studies MA 8.9yrs 32 M (upper & lower dysphagia) N=25 healthy adults	P-HRM-I 25P12Z	10 x 3-10ml saline	Chicago Classification (CC) + Oesophageal Pressure Flow Analysis (PFA)	CC metrics especially IRP 4s and distal latency are age and size dependent and therefor require adjustment to improve accuracy of diagnosis of oesophageal motility disorders in children.
High-Resolution Manometry Combined with Impedance Measurements Discriminates the Cause of Dysphagia in Children (208)					

Rommel et al, 2015	n=35 (17 M) MA 10.5 yrs Broad dysphagia (GERD, post-fundoplication, unknown aetiology) n=25 healthy controls (7 M) MA 36 yrs	3.2 mm High resolution impedance manometry solid state catheter 36 pressure sensors and 12 impedance electrodes	5-minute accommodation period Max 10 boluses 5ml saline and 5ml viscous (Sandhill Scientific) via syringe	-Oesophageal Peak Pressure -Pressure at Nadir Impedance -Intra-bolus pressure IBP slope -Time from nadir impedance to peak pressure -Pressure Flow Index	Reports first use of HRM with combined impedance in children. Revealed subtle abnormalities of oesophageal function which may not be detected with other assessment. Children with post-fundoplication dysphagia have different motor responses to bolus movement compared to the other children with dysphagia – a shorter time was observed between oesophageal maximal distension and peak bolus pressure, indicating a more pressurised bolus travelling through the oesophagus. Overall dysphagia patients show an increased PFI in the distal oesophagus. A promising new tool for clinical interpretation of medical interventions.
Pressure-Flow Characteristics of Normal and Disordered Esophageal Motor Patterns (186)					
Singendonk et al, 2015	n=76 (32 M) oesophageal disorders MA 9 yrs n=25 (7 M) healthy adult controls MA 36 yrs	3.2 mm High resolution impedance manometry with solid state catheter 25 pressure and 12 impedance channels Symptom checklist (DAKKAK score)	10 x liquid (saline) and 10 x viscous (Sandhill jelly) boluses (3-10mls depending on patient size and tolerance)	-Oesophageal peak pressure -Median intra-bolus pressure -Oesophageal Pressure at nadir impedance -Intra-bolus pressure slope (rate of change) -Time from nadir impedance to peak pressure -Impedance ratio (nadir impedance: impedance at Peak P)	Pressure flow characteristics of normal and disordered oesophageal motor patterns in children, whereby viscous swallows were more discriminatory of disordered swallowing compared to liquid swallows. Disordered oesophageal motor patterns were associated with altered PF characteristics. By defining the degree of over-pressurisation and/or extent of clearance failure, PFA may be a useful adjunct to oesophageal pressure topography-based classification of primary oesophageal motor disorders. It is shown that EGJ outflow obstruction will be

			Controls received 5 x 5ml and 5 x 10ml saline and viscous	-Pressure Flow Index (composite measure of bolus pressurization relative to flow -Chicago Classification and -- Oesophageal Pressure Topography Metrics	over diagnosed without adjusted paediatric specific criteria. In clinical settings simplified categorisation using composite scores: PFI and IR may help to guide treatment strategies.
Upper and Lower Esophageal Sphincter Kinetics are Modified During Maturation Effect of Pharyngeal Stimulus in Premature Infants (342)					
Jadcherla et al, 2015	n=24 very pre-term infants PMA 28 weeks n=12 pre-term infants PMA 35 weeks	Micromanometry water perfused system with UOS and LOS Dentsleeves	Mid oesophageal air and liquid administration (0.1-2.0mls)	Manometric wave form analysis: -UOS & LOS resting pressures -UOS contractile reflex -UOS CR latency -UOS CR duration -UOS CR magnitude -LOS relaxation onset -LOS relaxation latency -Active LOS relaxation duration -LOS relaxation reflex (RR) magnitude -LOS RR nadir duration	Gestational and postnatal modulation in UOS reflexes in human neonates when studied at term show subtle aerodigestive differences. Very premature infants showed prolonged UOSCR and LOSCR response durations, compared to premature infants. UOS contractile reflex duration similar to premature infants in line with the development of afferent and efferent excitatory pathways. UOS and LOS aerodigestive protective reflexes undergo maturation with gestational age.
Pressure Flow Analysis for the Assessment of Pediatric Oropharyngeal Dysphagia (55)					

Ferris et al, 2016	n=45 (26 M) MA 5 yrs Aspiration risk patients (neurological, metabolic, tracheostomy)	3.2 mm high resolution impedance manometry solid state catheter with 25 pressure sensors and 12 impedance electrodes	Liquid (saline) at least 3 x (2-5) ml swallows Controls at least 4 x 5ml liquid (saline) swallows	-Pharyngeal peak pressure -Pressure at nadir impedance -Time from bolus distension to peak pressure -Flow interval -UOS nadir impedance -UOS intra-bolus pressure during relaxation (resistance) -Post swallow impedance ratio	Pressure flow metrics were significantly altered in correlation with the abnormal Dysphagia Disorders Survey criteria for clinical signs of OPD, and a reduced measure of functional oral intake scale (FOIS) as seen among patients with worse aspiration risk. Comparing patients and controls, key differences in UOS resistance, and UOS distension were found, consistent with reduced UOS relaxation and opening in patients with oropharyngeal dysphagia. PFA offers objective profiling of bolus timing and efficiency of bolus clearance with integrated recordings of pressure activity in the pharynx and UOS. PFA findings suggest a greater prevalence of UOS dysfunction in paediatric patients with OPD, which could be targeted for therapy. PFA is a promising research tool that may, have the potential to clinically assess pharyngeal and UOS motor function during swallowing.
Pediatric Rumination Subtypes: A Study using High-Resolution Esophageal Manometry with Impedance (385)					
Rosen et al, 2017	n=21 (15 F) MA 15±4.9yrs (7-18yrs) Intractable regurgitation despite acid	36 high- resolution pressure ports and 12 impedance sensors Medtronics (Minneapolis Minnesota) or Laborie (Williston, VT)	10 x 5ml saline swallows 10 x 5ml viscous swallows Home meal eaten over 15	- R waves (high amplitude spikes in pressure seen in both the stomach and the oesophagus in the absence of cough) -Primary rumination if R wave triggered bolus movement into the oesophagus -Secondary rumination if R wave triggered after bolus movement into the oesophagus	High-resolution manometry with impedance is likely a useful tool for diagnosing rumination syndrome as it detects R waves and bolus flow into the oesophagus. Rumination subtypes are defined relative to LOS relaxation. Most rumination events occur immediately after a LOS relaxation, even when reflux is not occurring.

	suppression therapy. Pts remained on PPIs for testing.		mins followed by 30 minutes observation.	- Relationship of R waves to LOS relaxations - Relationship of R waves to retrograde bolus movement into the oesophagus visualised by impedance - Gastric pressures - LOS pressures - Thoracic pressures - Timing measures i.e. R wave to bolus entry, bolus presence to R wave, duration bolus presence in oesophagus - Extent of bolus ascent - Symptoms/sensation before R wave	
High-Resolution Esophageal Manometry Patterns in Children and Adolescents with Rumination Syndrome (386)					
Grunder et al, 2017	n=15 <18 yrs All participants fulfilled the Rome III criteria for rumination syndrome n=15 sex matched controls with	4.2 mm 360 circumferential high-resolution oesophageal manometry with solid state catheter 36 pressure channels and 12 radial pressure sensing points	2-minute period to assess basal sphincter pressures. 10 x 5ml tap water 100ml multiple swallow test	Manoview Analysis software version 2.0.1 -Rumination episodes – expulsion of gastric content without retching, pain, nausea, vomiting With or without TLOSR	To confirm diagnosis of rumination syndrome in children and adolescents, HROM patterns are a less invasive, more readily available technique compared to antroduodenal manometry. HROM investigations in this study confirmed diagnosis of rumination in 80% of participants. HROM may provide a pathophysiological explanation to children and their parents. Further research is needed to determine whether HROM results influence treatment and outcomes for children with rumination syndrome.

	near normal Chicago classification HREM studies		Test meal (Jello, cookies, or trigger aliment)		
Maturation Modulates Pharyngeal-Stimulus Provoked Pharyngeal and Respiratory Rhythms in Human Infants (222)					
Hasenstab et al, 2018	n=18 (11 M) Longitudinal study Healthy neonates Time 1: PMA 39.8 weeks Time 2: PMA 44 weeks	Water perfusion manometry Custom designed catheter with Dentsleeve.	Pharyngeal provocation induced rhythms with sterile water 0.1 – 0.5ml as tolerated and given in triplicates	-Prevalence of primary response to pharyngeal infusion (within 5 s of provocation) % -Composite pharyngeal response Split into two groups: Initial pharyngeal Response (tight cluster) Subsequent pharyngeal response (slower unclustered) -UOS contraction -Multiple pharyngeal swallow response 1 Magnitude (# and duration of pharyngeal peaks) 2 Frequency (# / duration)	This study investigated the maturational physiology of pharyngeal stimulation induced aerodigestive responses over 2 visits, with re-evaluation when infants had graduated to safe oral feeding. With advancing maturation deglutition apnoea duration decreases, the number of pharyngeal waveform peaks and duration decreases and stability increases. With increasing volumes there was a higher prevalence of initial and subsequent cluster responses. These changes are likely due to brainstem maturation, sensory and motor maturation of afferent and efferent pathway responses. These changes allow for safer swallowing with less chance of aspiration.

				3 Variability as standard deviation of pharyngeal peak to peak interval durations 4 Stability as Standard deviation of pharyngeal peak to peak interval durations (#) -Oesophageal body inhibition	
Novel Pressure-Impedance Parameters for Evaluating Esophageal Function in Pediatric Achalasia (187)					
Singendonk et al, 2018	n=20 achalasia patients (clinical diagnosis + fulfilling Chicago classification V3.0 criteria) 15 patients with normal	3.2- or 4.2-mm High resolution impedance manometry solid state catheter (depending on patient age or height) 36 pressure sensors and 18 adjoining impedance segments	10 x 5ml saline via syringe	Pressure Flow analysis metrics: -Oesophageal peak pressure -Oesophageal intra-bolus pressure -Impedance ratio (nadir impedance: peak pressure impedance) *Unable to define these metrics for achalasia type 1 patients Guided by impedance: -EGJ bolus presence (>50% drop from baseline)	The aim of this study was to evaluate oesophageal motor function in children diagnosed with achalasia using novel oesophageal pressure-flow variables. Findings support that in children, some metrics measured at the EGJ, BFT in particular, provide added information on EGJ outflow obstruction. Novel integrated Pressure-flow variables may have additional value for diagnostic assessment and monitoring of therapeutic efficacy. Further studies are needed to correlate these parameters with symptom severity before and after therapy.

	oesophageal motility			-Duration of bolus presence within EGJ (bolus presence time) -Trans EGJ bolus flow time (BFT) – summing criteria for BPT and subtracting time periods for crural contraction -Effectiveness of EGJ emptying (BFT/BPT) *10th %ile BFT and BPT in 'normal oesophageal HRM recordings' defined normal reference range.	
A Study of Dysphagia Symptoms and Esophageal Body Function in Children Undergoing Anti-Reflux Surgery (387)					
Omari et al, 2018	n=13 MA 6.8 yrs Pre & post 360 ° Nissen fundoplication	3.2 mm High resolution impedance manometry catheter with 25 pressure channels and 12 impedance segments	5-10 x 5ml boluses liquid (saline) and viscous (EFT Sandhill Scientific Jelly) 3-5 x 2 cm bread pieces with saline topically added to improve conductivity	Chicago Classification V3.0: -4 sec Integrated relaxation pressure (IRP 4 mmHg) -Contractile front velocity of distal oesophagus (CFV cm/s) -Distal contractile integral (DCI mmHg cm/s) -Distal latency (DL s) -EGJ contractile index (EGJ CI) -Subtype characterization: Type 1 (no LOS to crural diaphragm separation) Type 2 (partial	Dysphagia symptoms were common in paediatric GOR disease patients prior to anti-reflux surgery. In order to avoid symptom recurrence, re-evaluation and further interventions, dysphagia symptoms should be confirmed as being caused by GOR. In patients with normal motility, elevated clearance pressures and/or PFI may predict post-operative dysphagia. The findings were: (i) patients reported symptoms of dysphagia pre-operatively; (ii) fundoplication surgery decreased dysphagia in most; however (iii) some had post-operative dysphagia and were distinguishable by elevated bolus clearing pressures. Patients with manometry evidence of primary GOR disease (low OGJ-CI, hiatus hernia OGJ morphology and/or an IEM subtype) did not have post-operative

separation)

Type 3 (full separation)

Pressure Flow Analysis:

-Intra-bolus distension pressure (pressure at nadir impedance)

-Distension pressure bolus accommodation (UOS pressures to transition zone TZ)

-Distension pressure compartmentalised transport (TZ pressures to contractile deceleration point CDP)

-Distension pressure oesophageal emptying (pressures from CDP to crural diaphragm)

-Bolus clearance (impedance ratio)

-Bolus flow latencies (pressure and impedance at CDP including distension contraction latency and swallow to distension latency)

-Pressure generation during bolus clearance (pressure at luminal closure, and ramp pressure i.e. during closure)

-Pressure Flow Index (composite score amplifying dysfunction metrics)

-Trans OGJ bolus flow time

dysphagia. Patients with a normal motility diagnosis and higher clearing pressures had higher post-operative dysphagia scores. This association has been previously reported in post- operative and non-obstructive dysphagia (note, defined by the parameter ‘intra-bolus pressure slope’).

Piecemeal Deglutition and the Implications for Pressure Impedance Dysphagia Assessment in Pediatrics (184)					
Ferris et al, 2018	n=27 (19 M) MA 15 months Oesophageal atresia type IIIb Cohort grouped: G1 - < 12 mo G2: 1-4 yrs	2.7 mm High resolution impedance manometry solid state catheter with 32 pressure sensors and 16 impedance channels NB: impedance data converted to the inverse = admittance values	2-5ml liquid (saline) given via syringe	Piecemeal deglutition methodology: Selection of swallow sequences up to a max of 5 swallows within a 15 second window. Dominant swallows defined as largest volume within sequence guided by largest admittance peak and value. Pressure Flow Analysis variables: -Velopharyngeal tongue base contractile integral -Pharyngeal peak pressure -UOS post relaxation peak pressure -Distension contraction latency -hypopharyngeal intra-bolus pressure -UOS maximal admittance (max luminal cross-sectional area) -UOS basal pressure -UOS relaxation pressure -UOS integrated relaxation pressure (IRP) -UOS open time	Piecemeal deglutition (PD) with fewer swallows in a sequence led to higher velopharyngeal contractility; wider UOS distension diameter; longer UOS open time; lower UOS relaxation pressure; and longer pharyngeal distension contraction latency – all consistent with larger bolus volume with few swallows in a sequence. Importantly, without consideration for piecemeal deglutition during P-HRM-I analysis, a low UOS admittance value could be misinterpreted as impaired UOS opening when in fact it is caused by the reduced bolus volume associated with PD. Age related differences were greater UOS distension diameter; lower UOS relaxation pressures; longer distension contraction latency and higher hypopharyngeal intra-bolus pressure in older children – all consistent with a larger pharyngeal chamber compared to infants. The dominant swallow within a piecemeal sequence provides a meaningful analysis of swallowing function and is simpler to perform than averaged PD data.

Defining Pharyngeal Contractile Integral During High-Resolution Manometry in Neonates: A Neuromotor Marker of Pharyngeal Vigor (236)					
Jadcherla et al, 2018	n=19 thriving infants (12M, 34-41 weeks)	HRM 6Fr Unidirectional + 5Fr infusion catheter	Resting state for 10 spont. Swallows 0.3ml saline for infusions Bottle feeding session over 3 mins	Pharyngeal Contractile Integral (PhCI) via automated method	PhCI increased with sequential swallows from stimuli, remained stable during oral feeding. PhCI is distinct in the proximal and distal regions.
Pharyngeal Contractile and Regulatory Characteristics are Distinct During Nutritive Oral Stimulus in Preterm-Born Infants: Implications for Clinical and Research Applications (388)					

Prabhakar et al, 2019	n=41 infants (18 male)
	preterm or full-term gestation, measured at ≥40 weeks post menstrual age, some oral feeding occurring for inclusion
		6 Fr solid state catheter 25 unidirectional pressure sensors 1 cm apart (UniTip High-Resolution Catheter, Unisensor USA)	3-minute oral feeding challenge, after adjustment to the catheter.	- Pharyngeal contractile characteristics (PhCI)
				- Regulation of pharyngeal contractility:
				  - Solitary
				  - Bursts (2 or more occurring within 2 seconds)
				  - Number of contractions
				  - % contractile activity
				  - Activity to quiescence ratio
				  - Frequency of contractions
				  - Number of bursts
				  - Duration of bursts
					Preterm infants have reduced levels of milk extraction rates and pharyngeal activity compared to full-term infants. Despite longer oral nutritive experiences in pre-term compared to full-term infants, pre-term infants had underdeveloped excitatory and inhibitory rhythmic activity, suggesting cranial nerve IX and X remain underdeveloped in pre-term infants even at term age.

				- UOS relaxation - UOS nadir pressure	
Characterization of esophageal motility and esophagogastric junction in preterm infants with bronchopulmonary dysplasia (BPD) (343)					
Rayyan et al, 2020	n=28 premature infants with BPD (16 male) Studied at 40 weeks PMA (37-44) n=13 controls (10 healthy preterm, 3 term infants)	8 Fr solid state catheter 2.7 mm (13P 6Z)	Bottle feeding of expressed breast milk (EBM) or formula with saline added for conductivity (1/10 dilution of NaCl 0.9%). 0.5ml boluses administered by syringe if bottle feeding unsuccessful.	Oesophageal parameters: - Distal contractile integral - Distal latency - Integrated relaxation pressure (IRP) 4 - Intrabolus pressure during oesophageal emptying - Impedance ratio - Contractile segment impedance - EGJ mean resting pressure	Normal oesophageal peristalsis patterns were observed in preterm infant with BPD during nutritive swallowing, however increased flow resistance was observed at the EGJ relating to increased contractility of the diaphragm in these patients with BPD.
Maturation of Esophageal Motility and Esophagogastric Junction in Preterm Infants (390)					
Rayyan et al, 2020	n=10 healthy preterm infants (mean GA at birth 30 weeks) Supplemental NG feeding was the inclusion criteria.	8 Fr solid state catheter 2.7 mm (13P 6Z)	6 infants underwent all weekly motility studies over 4 weeks 4 infants underwent weekly motility studies over 3 weeks	Oesophageal parameters: - Distal contractile integral - Distal contractile velocity - Distal latency - Contractile deceleration point - Integrated relaxation pressure (IRP) 4 - Intrabolus pressure during oesophageal emptying - Bolus flow latencies: Swallow to distension latency	Oesophageal peristaltic contractions become faster, and the extent of EGJ relaxation reduces with maturational age in preterm infants.

			Bottle feeding of EBM or formula (1/10 dilution of NaCl 0.9%). 0.5ml boluses administered by syringe if bottle feeding unsuccessful.	Distension to contraction latency - Impedance ratio - Contractile segment impedance - EGJ mean resting pressure	
Mechanisms of Bradycardia in Premature Infants: Aerodigestive–Cardiac Regulatory–Rhythm Interactions (389)					
Hasenstab-Kenney et al, 2020	n=40 premature infants (23 male) 27 ± 3 weeks gestation n=28 recurrent bradycardia n=12 controls	Water perfused pharyngo-esophageal manometry, electrocardiography, respiratory inductance plethysmography and nasal airflow thermistor	Pharyngeal provocation	- Regional response latency - Response duration Each of these measurements taken in the pharynx, oesophagus, LOS, heart and respiratory system Additional measurements: - Total pharyngeal peaks per stimulus - Frequency (Hz) - Variability (s) - Terminal swallow prevalence (%) - Oesophageal inhibition - Oesophageal terminal swallow prevalence (%) - LOS basal tone - Relaxation prevalence - Nadir relaxation	Control infants and those with recurrent bradycardia show similar pharyngo-esophageal cardio respiratory (PECR) responses to pharyngeal provocation. However, PECR responses in severe bradycardia spells lead to abnormally long cardiorespiratory rhythms and prolonged oesophageal inhibition and delayed terminal swallowing.

Appendix 7

Preparation of Standard Bolus Medium (SBM)*kit*

HRIM Investigations

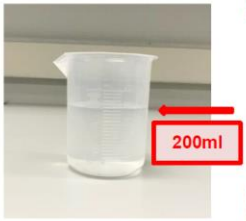
Please scan QR Code to view SBM preparation

Process

1

Add 6 pumps of **Precise SBM*kit* Saline Concentrate** to the measuring cup provided.

Twist the pump plunger anti-clockwise to release it from the stem.



2

Fill the cup to the 200ml level with tap water#

For liquid barium (e.g. Liquibar) add 20ml then fill to 200ml level. Note: the thickness and radio-opacity of liquid barium preparations can vary, independent testing to verify the optimal texture level is recommended.

3

Shake the Precise THICK'N bottle by inverting it 2-3times before opening the bottle

Add No. of pumps for Viscosity level required per table below.

	Viscosity Level Required				
	IDDSI 0*	IDDSI 1	IDDSI 2	IDDSI 3	IDDSI 4*
	Thin Liquid	Slightly Thick	Mildly Thick	Moderately Thick	Extremely Thick
No Pumps of Precise Thick N	0	1	2	4	6

*Textures recommended for HRIM investigations

4

Stir for 30 seconds

Stand for 5 minutes

Appendix 8

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If there are more than four co-authors (student plus 3 others), only the three co-authors with the most significant contributions are required to sign below.

Please note: A copy of this page will be provided to the Examiners.

1. Full publication Details: Pharyngeal manometry in pediatric dysphagia assessment. Perspectives of the ASHA Special Interest Groups. 2019; 4(4):656-82.

Section of the thesis where the publication is referred to: Chapter 2: Pharyngeal and UES swallow physiology captured by High-Resolution Manometry

Student's Contribution to the publication:

Research Design 50 %

Data Collection and analysis 0 %

Writing and editing 80 %

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Excerpts from this invited review of the literature have been incorporated in Chapter 2.

I was solely responsible for noting and collating the relevant literature included in this publication.

I produced the first draft and continued to refine the work with the input of principal supervisor, Taher Omari.

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