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Adaptation of the Functional Lumen Imaging Probe for Non-Radiological Evaluation of the Upper Oesophageal Sphincter

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A dissertation submitted to the University of Dublin for the degree of

Doctor of Philosophy

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February 2014

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Declaration

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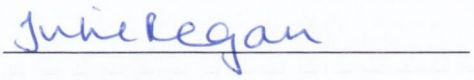

Julie Regan

February 28th, 2014

SUMMARY

The aim of this research was to adapt the Functional Lumen Imaging Probe (FLIP), a novel non-radiological measurement tool, to measure upper oesophageal sphincter (UOS) distensibility and opening patterns during swallowing. Initially, accuracy of EndoFLIP® (a commercial FLIP device) measures was investigated and the safe insertion, positioning and distension of the EndoFLIP® balloon was tested by the researcher in the UOS of two subjects with dysphagia under videofluoroscopy (VFS). Five pilot studies were subsequently completed without VFS guidance during which the EndoFLIP® probe was inserted trans-orally. Based on these studies, the researcher designed an evaluation protocol and defined outcome measures.

In a group of fourteen non-elderly (20-50 years) healthy subjects, UOS distensibility was evaluated using EndoFLIP®. Thirteen subjects tolerated the study protocol. UOS cross-sectional area (CSA) ($p<.001$) and intra-balloon pressure (IBP) ($p<.001$) altered significantly during distensibility testing. UOS CSA increased significantly between 1ml and 5ml ($p=0.028$) and from 5ml to 10ml ($p<.001$) balloon volumes, from which point the UOS resisted further distension. IBP increased significantly from 10ml to 15ml ($p=0.004$) and from 15ml to 20ml balloon volumes ($p=0.003$), indicating adequate UOS tone in this group. UOS CSA was significantly larger in females at 1 and 5ml balloon volumes ($p=0.004$ and 0.005 respectively). An increase in IBP in males at 5, 10 and 15ml balloon volumes was statistically significant.

In the same subject group, the researcher measured extent of UOS opening across dry (9.6mm), 5ml (8.61mm) and 10ml liquid swallows (8.27mm) using EndoFLIP® ($n=14$). UOS opening duration was 0.5 seconds across bolus volumes ($p=0.91$). Minimum IBP dropped from a baseline of 18.8mmHg during dry (3.6mmHg), 5ml (4.8mmHg) and 10ml liquid swallows (2.96mmHg). FLIP UOS measures were comparable to previous VFS findings. UOS diameter was significantly larger in females (9.85mm) than in males (9.46mm) during dry swallows ($p=0.043$), whereas a significantly larger drop in IBP was observed in males than in females during 5ml

(3.36mmHg and 7.08mmHg; p=0.043) and 10ml liquid swallows (2.64mmHg and 6.22mmHg; p=0.043). EndoFLIP® data was used to create colour contour plots to visualise UOS opening patterns.

According to EndoFLIP®, voluntary postures and manoeuvres significantly affected extent (p=0.0126) and duration of UOS opening (p=0.0013) and minimum IBP during swallowing (p=0.0049) (n=11). Specifically, the Mendelsohn manoeuvre significantly increased duration of UOS opening (0.46-0.57secs; p=0.014) and the supraglottic swallow significantly reduced minimum IBP during swallowing (4.55--0.13mmHg; p=0.023).

The researcher compared UOS opening measures during swallowing from EndoFLIP® to automated impedance manometry (AIM) analysis parameters based on combined high-resolution manometry and intra-luminal impedance (n=11). A significant interaction effect correlation was observed between EndoFLIP® extent of UOS opening and pressure at nadir impedance (p=0.034) and between EndoFLIP® UOS opening duration and UOS relaxation interval (RI) (p=0.0272).

In a clinical study, FLIP evaluated distensibility of the surgically reconstructed pharyngo-oesophageal segment (POS) in ten total laryngectomy patients (70% tolerance rate observed). A significant increase in POS CSA throughout the 20ml ramp distension (p<0.001) indicated reduced POS tone. Extent of POS opening during swallowing was reduced (albeit statistically insignificant) and duration of POS opening during swallowing was significantly longer across dry (p=0.028), 5ml (p=0.034) and 10ml (p=0.027) liquid swallows in this clinical group compared to healthy controls.

Finally, in an international 25-item online survey, the researcher found that just 17.9% (40/224) of dysphagia-trained SLTs are satisfied with current methods to evaluate the UOS.

This work contributes original quantitative information pertaining to UOS distensibility and opening patterns during swallowing. Improved UOS evaluation is necessary to improve our understanding of the UOS and to develop evidence-based dysphagia treatments. Directions for future research are proposed to complete the validation of EndoFLIP® in UOS evaluation.

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ACKNOWLEDGEMENTS

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NOMENCLATURE

2-D	2-dimensional
3-D	3-dimensional
AGA	American Gastroenterological Association
AIM	automated impedance manometry
AP	anterior-posterior
ASHA	American Speech and Hearing Association
Ax	assessment
Ba	barium
BoNT-A	botulinum toxin A
BSE	bedside swallow evaluation
CP	cricopharyngeus
CSA	cross-sectional area
CT	computed tomography
DA	diagnostic accuracy
Dest	estimated diameter
EMG	electromyography
ENT	Ear Nose and Throat
FEES	fiberoptic endoscopic evaluation of swallowing
FLIP	functional lumen imaging probe
FOAMS	functional outcome assessment measure of swallowing
GI	gastro-intestinal
GORD	gastro-oesophageal reflux disease
H&N Ca	head and neck cancer
H-LA	hyo-laryngeal approximation
HRM	high resolution manometry
IASLT	Irish Association of Speech & Language Therapists
IBP	intra-balloon pressure
IMRT	intensity modulated radiotherapy
IP	impedance planimetry
IPC	inferior pharyngeal constrictor
IQR	inter-quartile range
LRTI	lower respiratory tract infection
MDT	multidisciplinary team
MII	multichannel intra-luminal impedance

minIBP	minimum intra-balloon pressure
mm	millimetre
mmHg	pressure
ml	millilitre
mths	months
NaCl	sodium chloride
NMES	neuromuscular electrical stimulation
NPO	nil per oral
OGD	oesophagastro- duodenoscope
OGJ	oesopho-gastric junction
OM	oesophageal manometry
PAS	penetration-aspiration scale
PCR	pharyngeal constriction ratio
PEG	percutaneous gastrostomy
PD	parkinson's disease
PM	pharyngeal manometry
POS	pharyngo-oesophageal segment
QUADAS	quality assessment of diagnostic accuracy studies
RCSLT	Royal College of Speech and Language Therapists
ROI	Republic of Ireland
SD	standard deviation
secs	seconds
sEMG	surface electromyography
SIG	special interest group
SLT	speech and language therapist
TC	trans-cutaneous
TNO	trans-nasal oesophagoscopy
Tx	treatment
UOS	upper oesophageal sphincter
VC	vocal cords
VFS	videofluoroscopy
Vol	volume
yrs	years

PUBLICATIONS AND PRESENTATIONS

Work arising from this thesis which has been published in peer-reviewed papers to date (see Appendix 10):

Regan, J., Walshe, M. and McMahon, B. P. (2012), Current evaluation of upper oesophageal sphincter opening in dysphagia practice: an international SLT survey. International Journal of Language & Communication Disorders, 47 (2): 156–165.

Regan, J., Walshe, M., Rommel, N. and McMahon, B. P. (2013), A new evaluation of the upper esophageal sphincter using the functional lumen imaging probe: a preliminary report. Diseases of the Esophagus. 26 (2): 117-123.

Regan J, Walshe M, Murphy A, McMahon BP, Coughlan T. Botulinum toxin for upper oesophageal sphincter dysfunction in neurological swallowing disorders (Protocol). Cochrane Database of Systematic Reviews 2012, Issue 7. Art. No.: CD009968. DOI: 10.1002/14651858.CD009968.

Regan, J., Walshe, M., Rommel, N., Tack, J. & McMahon, B. New measures of upper esophageal sphincter distensibility and opening patterns during swallowing in healthy subjects using EndoFLIP®. Neurogastroenterology & Motility. 2013 (25) 1: 25-34.

Book Chapters:

Regan, J. & Walshe, M. (2012) Neuromuscular Conditions. In Newman, R & Nightingale, J. (Eds.) *Videofluoroscopy: A Multi-Disciplinary Team Approach.* San Diego, Plural Publishing Inc. pp.177-195.

Regan, J. Texture Modified Diets. Ed. Ickenstein, G. in Diagnosis and treatment of neurogenic dysphagia. UNI-MED Science, 1st edition 2011, 96 Seiten, 31 illustrations, Hardcover, ISBN 978-3-8374-1273-4.

The work in this thesis has been presented at the following international and national conferences (*invited):

Oral Presentations

Regan, J., Walshe, M. & B.P. McMahon. *Use of the functional Lumen Imaging Probe to Measure Upper Esophageal Sphincter Opening.* Dysphagia Research Society 18th Annual Conference. San Antonio, Texas. March 2011.

*Regan, J. Behavioural Treatment of Dysphagia- Postures and Manoeuvres. FRANC Dysphagia 2011 Fresenius Kabi Advanced Nutrition Course on Dysphagia. Bad Homburg, February 2011.

*Regan, J. Oral Nutrition in Dysphagia- A True Alternative. European Society for Parenteral and Enteral Nutrition (ESPEN), Nice, France. September 2010.

*Regan, J. Dysphagia Screening- A Substitute for Instrumental Evaluation of Swallowing? Oral Presentation at European Society of Swallowing Disorders (ESSD) 1st Annual Conference. Netherlands. September, 2011.

Regan, J., Walshe, M., Rommel, N. & McMahon, B. Use of the Functional Lumen Imaging Probe to Measure Upper Oesophageal Sphincter Opening During Swallowing. European Medical Physics and Engineering Conference (EMPEC), Trinity College Dublin, September, 2011.

Regan, J., Walshe, M. & B.P. McMahon. Evaluation of Upper Oesophageal Sphincter Opening- Room for Improvement. Irish Association of Speech & Language Therapists (IASLT) Biennial Conference. Galway, October 2009.

Regan J, Walshe M, Murphy A, McMahon BP, Coughlan T. Botulinum toxin for upper oesophageal sphincter dysfunction in neurological swallowing disorders- a systematic review. United Kingdom Swallow Research Group Conference. UCL Institute of Child Health, London, UK. February 2012.

Regan, J., Walshe, M., Rommel, N., Tack, J. & McMahon, B. Non-radiological measurement of extent and duration of upper oesophageal sphincter opening during Swallowing using EndoFLIP®. European Society of Swallowing Disorders (ESSD) 2nd Conference. Barcelona, 26th October 2012.

Poster Presentations (see Appendix 9)

Regan, J., Walshe, M. & B.P. McMahon. Working Towards an Objective and Reliable Evaluation of the Upper Esophageal Sphincter . United Kingdom Swallow Research Group (UKSRG). UCL Institute of Child Health, London, UK. 4-5th February 2010. (1st poster prize).

Regan, J., Walshe, M. & B.P. McMahon. Current Evaluation of the Upper Esophageal Sphincter in Neurogenic Dysphagia- A Survey, 6th Congress of the European Union Geriatric Medicine Society (EUGMS). Dublin, September 2010.

Regan, J., Walshe, M. & B.P. McMahon. Challenges in Evaluating the Upper Esophageal Sphincter in Dysphagia Practice- A Survey of SLPs. Dysphagia Research Society 18th Annual Conference. San Antonio, Texas. March 2011.

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CHAPTER 1. INTRODUCTION

CHAPTER 1. INTRODUCTION

1.1. Background

The aim of this research study is to adapt the Functional Lumen Imaging Probe (FLIP), a novel non-radiological measurement tool, for accurate and quantitative measurement of the upper oesophageal sphincter (UOS). This introductory chapter outlines the context of the project, provides a theoretical framework for examining this area and concludes with research questions and thesis structure.

Impaired UOS opening leads to difficulty eating, drinking and swallowing (***dysphagia***) and it has critical implications from a clinical viewpoint. Specifically, inadequate UOS opening can prevent a bolus from transferring safely and efficiently from the pharynx into the oesophagus during swallowing. Where there is increased resistance from the sphincter, a proportion of the bolus typically remains post swallow in the pyriform sinuses within the pharynx, which are located adjacent to the airway entrance. As the epiglottis returns to its resting position and the true and false vocal cords abduct to resume respiration post swallow, material sitting in the pyriform sinus can descend into the trachea. Redirection of material into the trachea below the level of the true vocal cords is defined as ***aspiration.*** Depending on the laryngeal sensation and reflexive cough response of the individual, aspirated material may or may not be ejected out of the trachea.

If aspirated material is not rejected from the trachea, aspiration pneumonia can ensue (typically in the right lung base). Aspiration pneumonia has an associated mortality of up to 50%, and hence needs to be avoided from both a clinical and healthcare providers viewpoint (1). Several independent risk factors for aspiration pneumonia beyond dysphagia have been identified which include impaired cognition, immobility, tube feeding, polypharmacy and need for assistance with feeding (2, 3). Aspiration and aspiration pneumonia are not the only clinical sequelae of pharyngo-oesophageal dysphagia. Other complications of dysphagia include weight

loss, malnutrition and dehydration (4). From a psychosocial perspective, dysphagia also has a marked impact on health-related quality of life (5-7).

These multiple complications can lead to increased morbidity and mortality, prolonged hospital stays, hospital readmissions, antibiotic cover, tube feeding and institutionalisation (4, 8, 9). Hence, dysphagia does not only have a huge impact on the individual, it also has significant financial implications from a healthcare service viewpoint. Up to 16% of the general population present with oro-pharyngeal dysphagia (10). This rate increases to 50% in the elderly (11). Dysphagia presents in 81% of people in the acute stages following stroke, while a similar percentage (80%) of individuals with Parkinson's Disease (PD) have symptoms of dysphagia (12, 13). Given the prevalence of dysphagia in acute and community healthcare settings and the potential clinical and healthcare implications, optimal dysphagia assessment and management is essential.

Currently, instrumental assessments such as videofluorosopy (VFS), fiberoptic endoscopic evaluation of swallowing (FEES) and pharyngeal manometry (PM) provide valuable information on UOS opening during swallowing in clinical practice. Despite this, the acquisition of objective and reliable measurements of extent and duration of UOS opening during swallowing and the ability to deduce the underlying cause of UOS dysfunction remain a challenge to dysphagia clinicians. As a result, clinicians often have great difficulty establishing candidacy for various treatments and in determining any benefit from these interventions. Additionally, existing UOS evaluations frequently involve radiation exposure; they can be labour intensive involving several members of the multidisciplinary team (MDT) and procedures are often time consuming to complete and to analyse. Material being swallowed is often not reflective of meal times due to the addition of barium contrast to the bolus and the lack of portability of current assessments can limit these procedures to individuals who are medically stable and mobile with good posture and positioning. In this research study, EndoFLIP® (a commercial FLIP device) is employed for the first time to obtain objective and reliable evaluation of the UOS at rest and during swallowing events.

1.2. Context of the study

The researcher is a speech and language therapist (SLT) with over twelve years clinical experience in the assessment and management of adults with acute and progressive oro-pharyngeal dysphagia in an acute hospital setting. Despite routine access to and advanced training in numerous instrumental dysphagia examinations (including VFS, FEES, PM and surface electromyography), reliable detection of the nature and severity of impaired UOS opening during swallowing consistently challenges the researcher, departmental colleagues, MDT members and professional colleagues internationally. A survey carried out by the researcher confirms this and will be reported later in Chapter 3.5.2. Specifically, the acquisition of objective and reliable data pertaining to UOS opening during swallowing and identification of the nature of UOS dysfunction eludes the majority of clinicians. As a result of this lack of clarity, the researcher has witnessed multiple cases where adults with dysphagia have had to endure intensive rehabilitation or surgical interventions, with potential adverse events, that were of no benefit to them. Alternatively, individuals who have not benefited from conservative rehabilitation have not been considered for more invasive interventions solely due to lack of objective candidacy criteria based on current instrumental examinations. The need for an objective and reliable evaluation tool which can accurately quantify parameters of swallowing and guide dysphagia treatment has not only been identified within clinical practice but also within dysphagia research (14-16). The development of such a tool is not impossible given that devices are already available (at least off-label at a research level) to evaluate other anatomical lumens (17-20). The adaptation of this tool to the UOS seemed to be one way of addressing this need.

1.3. Role of the Researcher within the Research Process

The development of a new clinical evaluation tool is by nature a MDT process, hence the involvement of a team including Medical Physics and Bioengineering, Gastroenterology technicians, nursing staff, medical staff and SLTs in this research. However, the researcher very much initiated and led each of the studies included in this research. The roles of the researcher

included the formulation of each of the research questions and corresponding hypotheses; the methodological design of each of the research studies; the development of novel study protocols for UOS testing and the identification of clinically relevant outcome measures specific to the UOS; the selection of probe balloons; the acquisition of ethical approval; the recruitment of healthy control and clinical subjects; the collection and analysis of all data acquired; the interpretation of results and discussion of findings.

1.4. Theoretical Framework

This research is based on the general hypothesis that the availability of a new objective and reliable diagnostic tool which can provide novel information on UOS opening should progress our understanding of UOS dysfunction. The advancement of UOS evaluation must ultimately lead to better dysphagia management including refined dysphagia intervention efficacy and candidacy criteria. This should reduce the numerous clinical and quality of life complications associated with dysphagia. These developments would benefit not just the individual but the health care settings involved.

The theoretical framework underpinning this project is that evaluation of UOS dysfunction is possible using a new diagnostic tool. This tool needs to be safe and it needs to provide accurate measurements. It should be able to obtain clinically useful measurements of the UOS in healthy adults and be able to evaluate the effects of interventions currently employed in dysphagia practice. The tool needs to be validated and should be clinically useful, both from the perspective of the individual with dysphagia and the clinician working in dysphagia practice. These requisites form the basis for the research questions in this project which are described in Chapter 1.5.

1.5. Research Questions

This research is based on four pre-determined research questions. These are:

1. Can EndoFLIP® provide accurate measures of the UOS and can it be safely positioned in the UOS in people with and without dysphagia to obtain measures of the UOS?
2. If yes, can EndoFLIP® provide normative data on UOS distensibility and UOS opening during swallowing in an adult healthy group?
3. How do EndoFLIP® measures of UOS opening during swallowing compare to an existing dysphagia evaluation such as High Resolution Manometry with Impedance?
4. What is the clinical utility of EndoFLIP® in dysphagia practice?

1.6. Structure of the Thesis

This thesis follows a traditional format and is divided into five central chapters. The overall structure of these chapters is outlined below.

1.6.1. Chapter 1 and 2– Introduction and Literature review

The background to the research is introduced, beginning with an introduction to EndoFLIP®, a novel method to evaluate anatomical lumens. Next, the UOS is described with a review of its anatomical structure, physiological function and the causes and nature of UOS dysfunction. Current evaluations of the UOS are described and limitations to these UOS evaluations are portrayed. The need for new novel objective information on UOS opening to complement existing evaluations in clinical practice is argued in order to advance our understanding of the UOS. The literature pertaining to the research is critically evaluated and the justification for the study is argued. Based on this literature review, study aims, research questions and hypotheses are posed for this research.

1.6.2. Chapter 3- Methodology

This chapter describes general methodological design of this research. To address the first research question, methods to test the accuracy of EndoFLIP® data are described. The researcher then reports testing the

safety of EndoFLIP® probe insertion and balloon distension in the UOS under VFS in two adults with dysphagia. Based on these findings, the researcher completed five pilot studies in a third study without videofluoroscopic guidance. The researcher subsequently developed a UOS evaluation study protocol and defined outcome measures for UOS evaluation. This leads into the second section where the methodology for research studies evaluating UOS function in fourteen healthy adults using EndoFLIP® are reported. UOS distensibility and UOS opening patterns during swallowing are investigated in this group and methods to evaluate gender differences are outlined. Methods to investigate the effects of postural strategies and manoeuvres on UOS opening during swallowing in this healthy group are described. To address the third research question, a study comparing EndoFLIP® measures of UOS opening during swallowing to UOS opening measures from an existing dysphagia evaluation is reported. Finally, in order to determine the clinical utility of EndoFLIP®, methods to evaluate UOS function in ten adults with laryngectomy using EndoFLIP® are described and methods to obtain feedback from dysphagia-trained SLTs regarding satisfaction with current UOS evaluation and the potential role of EndoFLIP® in dysphagia practice are reported.

1.6.3. Chapter 4- Results

The fourth chapter reports the results from each of the separate research studies described in Chapter 3. Accuracy and safety data is initially presented and results of pilot studies without VFS are provided. Findings on UOS distensibility and the extent and duration of UOS opening during swallowing in a healthy non-elderly subject group are reported. Gender differences in UOS distensibility and UOS opening during swallowing are presented. Results on the effects of voluntary postures and manoeuvres on UOS opening during swallowing are described based on EndoFLIP® findings. Next, the results of UOS evaluations using EndoFLIP® are compared to data obtained from combined high-resolution manometry (HRM) and multi-channel intra-luminal impedance (MII). Results from EndoFLIP® evaluations in ten adults with total laryngectomy are reported. Distensibility patterns in this clinical group are compared to UOS distensibility findings previously observed in healthy subjects. POS opening patterns during swallowing in

the total laryngectomy group are also quantified and compared to UOS opening measures from healthy subjects. Finally, satisfaction levels amongst dysphagia-trained SLTs internationally with current methods to evaluate UOS opening in dysphagia practice are provided and feedback from dysphagia clinicians regarding the potential role of EndoFLIP® in UOS evaluation is reported.

1.6.4. Chapter 5- Discussion

In the final chapter, the researcher explores major research findings and results from individual research studies, discussing these within the context of previous dysphagia research and current knowledge. Methodological issues based on research to date are deliberated and guidelines for future research are proposed. The current status of EndoFLIP® as a clinical dysphagia tool is debated and the long term goal of this research is considered.

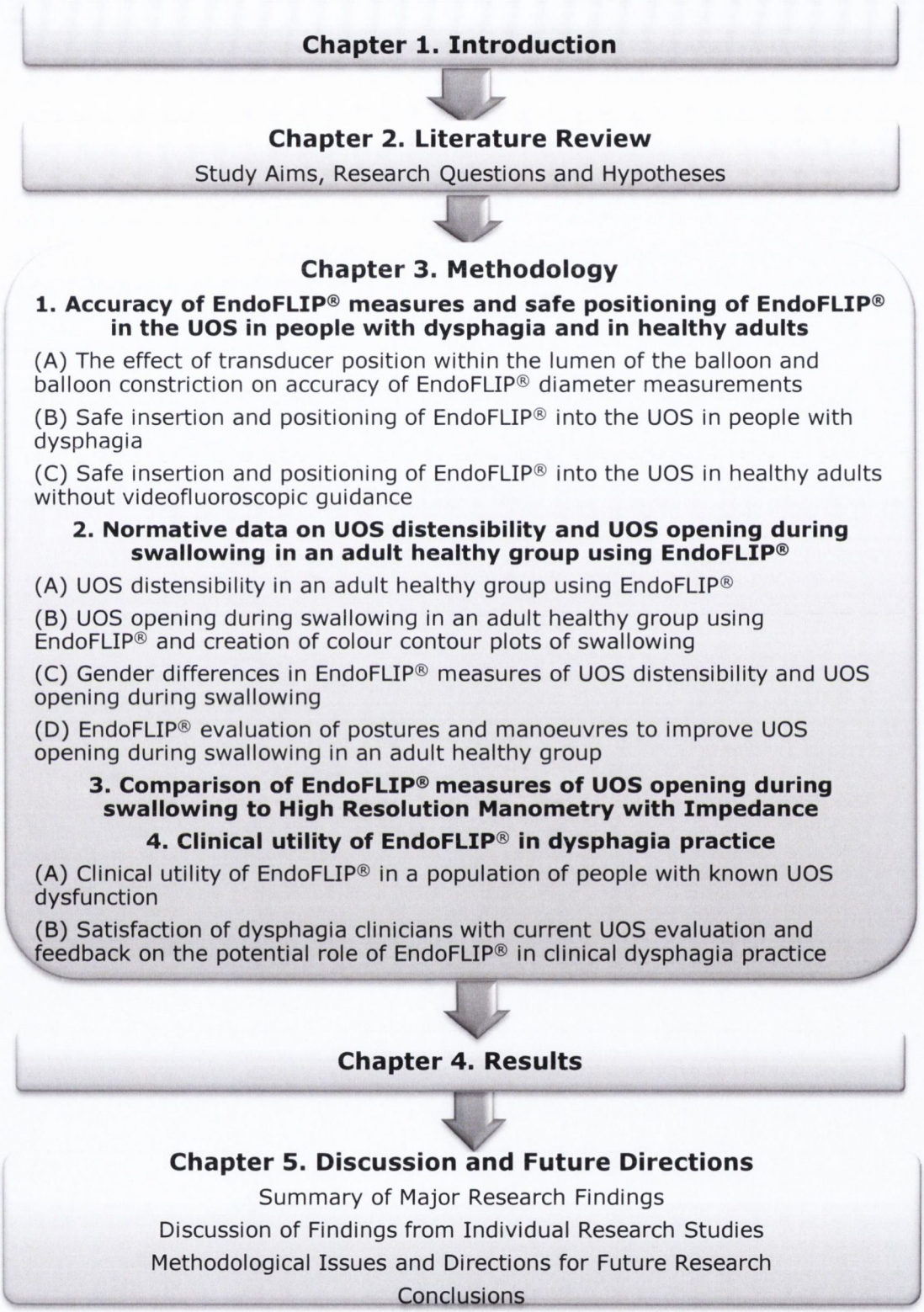

Figure 1.1 Thesis Outline

CHAPTER 2. LITERATURE REVIEW

2.0. INTRODUCTION TO LITERATURE REVIEW

The focus of this second chapter is to critically evaluate published literature pertaining to this research and to justify this research study. This chapter is divided into six key sections. In the first section, FLIP, a diagnostic tool designed to evaluate anatomical lumens, is described. The background to and measurements derived from this evaluation technique are described and its current roles in clinical practice and in research are reviewed.

In the second section, the UOS is defined and a summary of its anatomy and various physiological roles are provided. Mechanisms of UOS opening during normal swallowing are described as are factors affecting the extent and duration of UOS opening during swallowing. Understanding normal function is critical to understanding the patterns of impairment. Potential causes of impaired UOS opening during swallowing within commonly associated diagnostic groups are described in section three and the evidence base for clinical interventions currently employed by various members of the MDT to optimise and manage UOS opening are outlined in section four. Reliable identification of the cause and severity of the UOS dysfunction during diagnostic evaluation is critical to safe and beneficial dysphagia treatment.

In section five of this chapter, current instrumental methods employed clinically and in research domains to diagnose UOS dysfunction in individuals with dysphagia are critically reviewed according to their diagnostic accuracy, their utility as outcome measurement and their clinical and research limitations. Until UOS investigation advances, our understanding of UOS dysfunction and provision of optimal treatment will be limited. Finally, in section six, the potential role of FLIP in the evaluation of UOS dynamics is hypothesised. Research aims originally introduced in Chapter 1 are expanded and corresponding hypotheses are outlined.

CHAPTER 2.1. ENDOFLIP®- A FUNCTIONAL LUMEN IMAGING PROBE

2.1.1. Background

The Functional Lumen Imaging Probe (FLIP) is a novel non-radiological measurement tool capable of providing reliable quantitative data regarding sphincter function. In relation to videofluoroscopy, FLIP evaluations are simple and timesaving procedures which can be conducted at the bedside. By positioning and distending a fluid-filled balloon on the distal end of a probe in a lumen under evaluation, FLIP measures cross-sectional area (CSA) and intra-balloon pressure (IBP) to determine lumen distensibility (Figure 2.1).

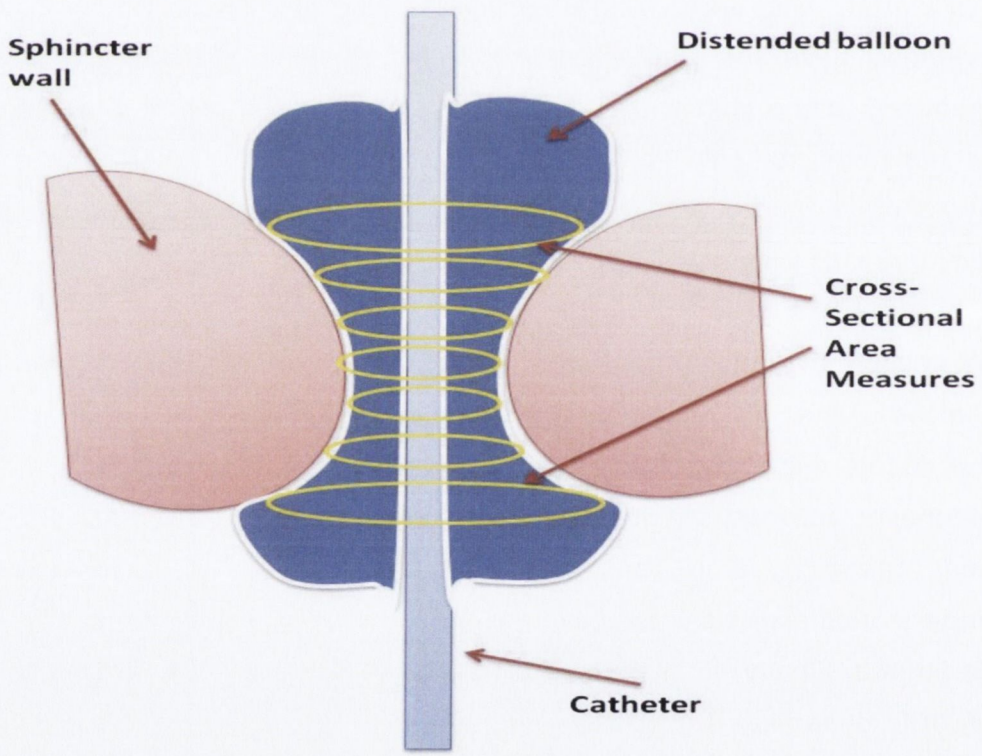

Figure 2.1 Multiple Cross-Sectional Area Measures within a Sphincter[1]

[1] In the context of this thesis, a balloon is synonymous with a non-compliant bag capable of being inflated without contributing to the resistance to inflation.

FLIP was originally designed to examine distensibility or compliance of the oesopho-gastric junction (OGJ) in individuals with achalasia and gastro-oesophageal reflux disease (GORD). As a result of its success, this evaluation has since been employed internationally to evaluate lumens at various anatomical sites beyond the OGJ. The principles underlying FLIP will now be described.

2.1.2. Principles underlying FLIP

There are three principal characteristics underlying FLIP. These principles are outlined below.

(a) Impedance Planimetry

Impedance planimetry (IP) (also termed the field grade principle or four-electrode technique) is a technique which measures CSA of a plane using electrical impedance measurements. Originally, this technique provided a single measure of CSA within the ureter (21). It was later developed to a stage where the impedance electrodes were placed in a fluid-filled latex balloon or bag to measure wall compliance (22). The balloon method was developed by Hans Gregersen for the evaluation of the gastrointestinal tract (23). Many studies have since shown the usefulness and reliability of IP in the oesophagus of animals, healthy volunteers and patients (24-28). Due to limitations, such as difficulty placing the measurement electrodes at the point of most interest and the fact that distending a balloon in a high-pressure zone tends to displace the balloon during the measurements, IP has only been used in a few studies in sphincter regions (29).

(b) Multiple Electrode Measurements

The concept of IP was further developed in 2005 by McMahon, Frøkjær, Liao, Kunwald, Drewes and Gregersen in a pilot study using a multi-electrode technique (17). An IP probe with five sensing electrode pairs (2mm between pairs and 2cms between sets) was constructed and placed in the porcine rectum (17). While there are several potential sources of error in multiple measurement IP systems (e.g., electrodes placed too close together will interfere with each other, potential for interference due to increased number of wires and liquid leaking into the probe), this technique

was successful in demonstrating how a balloon with a conducting liquid and a constant current source set up across two excitation electrodes can measure multiple CSAs by measuring the voltage across multiple electrode pairs within the electric field (Figure 2.1.).

(c) Measurement of Cross-Sectional-Area

McMahon, Frøkjær, Drewes and Gregersen (2004) subsequently demonstrated that a preliminary multi-electrode probe with a cylindrical balloon mounted and filled with saline could be distended in the OGJ of a healthy volunteer and that data from three CSAs could be derived (30). Limitations reported in this study included the inability of just three CSA measurements to profile the OGJ. To address this deficiency, a more elaborate probe with eight sensors was designed and constructed, which could provide quantitative measurement of eight CSAs within the OGJ of a healthy control subject (17). Methodological obstacles included the electrode and wiring assembly within a 1.7mm catheter, but these issues were overcome and the probe was capable of measuring eight CSAs at 4mm intervals, allowing the probe to span a range of 28mm (Figure 2.1). A major development was that the data derived could be exported and represented as a three dimensional image to profile the geometry of the OGJ (17). The probe described in this study led to a new evaluation tool known as the Functional Lumen Imaging Probe (FLIP)(17). The commercially developed FLIP is called the EndoFLIP® system (Crospon Ltd., Galway, Ireland) (Figure 2.2). The EndoFLIP® probe designed for OGJ evaluation consists of a catheter with a balloon positioned on the distal end. In this remainder of this thesis, the researcher will refer to the tool as EndoFLIP®.

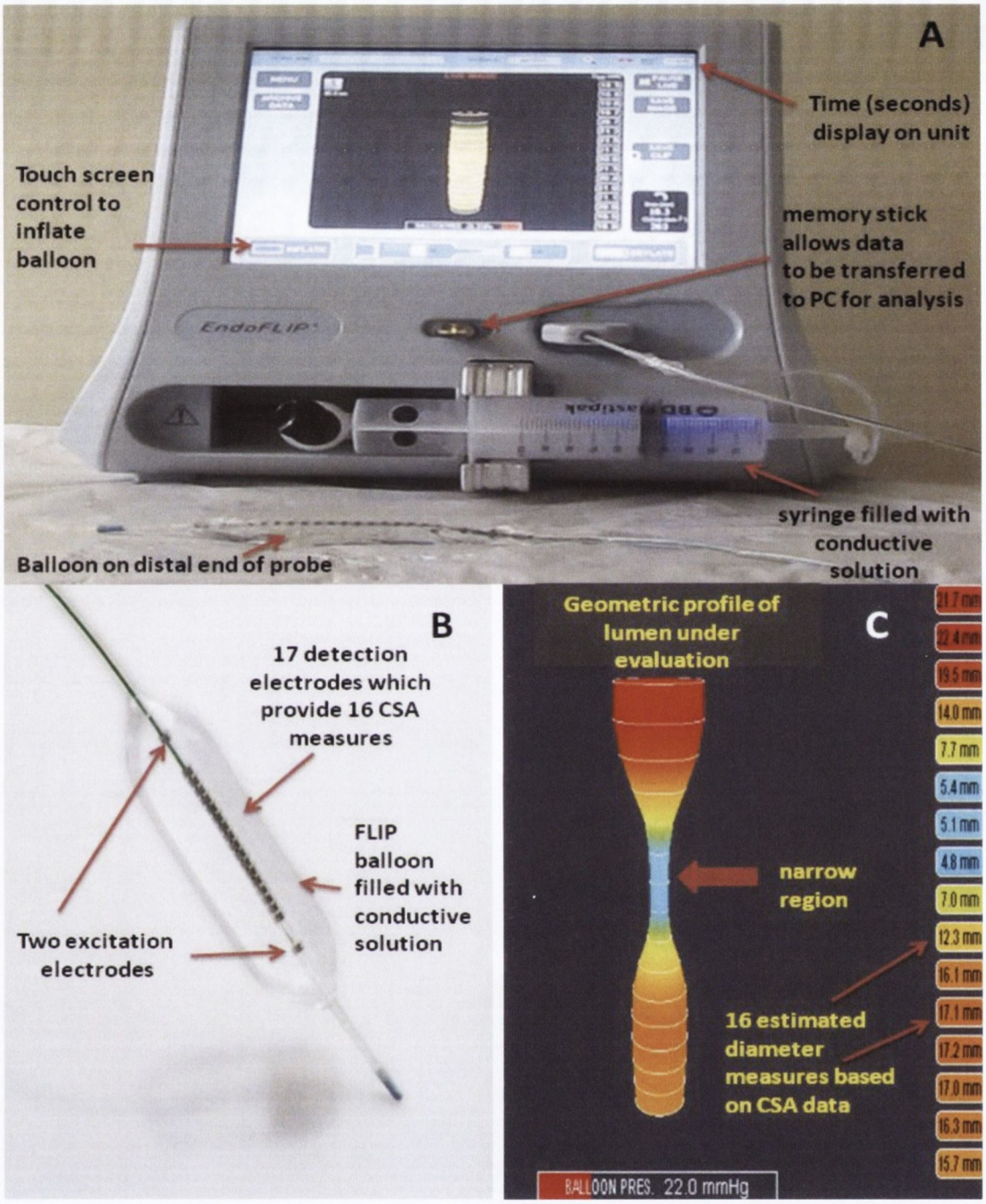

Figure 2.2 EndoFLIP® System[2]

[2] The EndoFLIP® balloon is positioned in the anatomical lumen of interest and distended for evaluation. This non-compliant balloon houses seventeen detection electrodes and an excitation electrode at both ends, which provide sixteen diameter measurements (B). When the conductive solution enters the balloon, estimated diameter (or CSA) measurements are taken from between each of the detection electrodes. This data is used to create a geometric profile of the lumen (C).

2.1.3. Distensibility Testing as a Measure of Sphincter Competence

Radiological and manometric tests have traditionally been employed to measure sphincter competence. However, distension of a valve or junction has been proposed as a superior method to evaluate valve performance. Harris and Pope (1964) observed that squeeze or contraction, which is measured by manometry, does not indicate a competent sphincter. Instead, resistance to distension is a determinant of sphincter strength (31).

2.1.4. How is Distensibility Tested?

Distensibility testing involves a challenge test by inflating a balloon which is positioned within the sphincter under evaluation (see Figure 2.2B). The response of that sphincter or valve to the balloon distension provides information regarding its distensibility. Those with reduced sphincter tone typically exhibit increased sphincter distensibility (e.g., OGJ in GORD), where the narrowest CSA within the lumen increases throughout the distension and IBP remains low. In contrast, those with increased sphincter tone (e.g., OGJ in achalasia) may present with reduced distensibility, with little change in the narrow CSA and an increase in IBP during testing.

Balloon distensions can be carried out in several ways. Both pressure and volume can be controlled in isobaric and isovolumetric protocols respectively (32). Distensions can be conducted as a staircase test, a step test or as a ramp test, depending on the purpose of the study (Figure 2.3). Ramp distensions will be completed to measure UOS distensibility in this research as they can be completed rapidly which is of importance to minimise any discomfort or airway impingement during testing. The biggest advantage of ramp distensions is a pure elastic response rather than a viscoelastic response (as observed in step or stair mechanical protocols). As human tissue needs to be pre-conditioned before responses become repeatable, catering for a habituation effect is important in distension testing and this should be considered within distension study protocols.

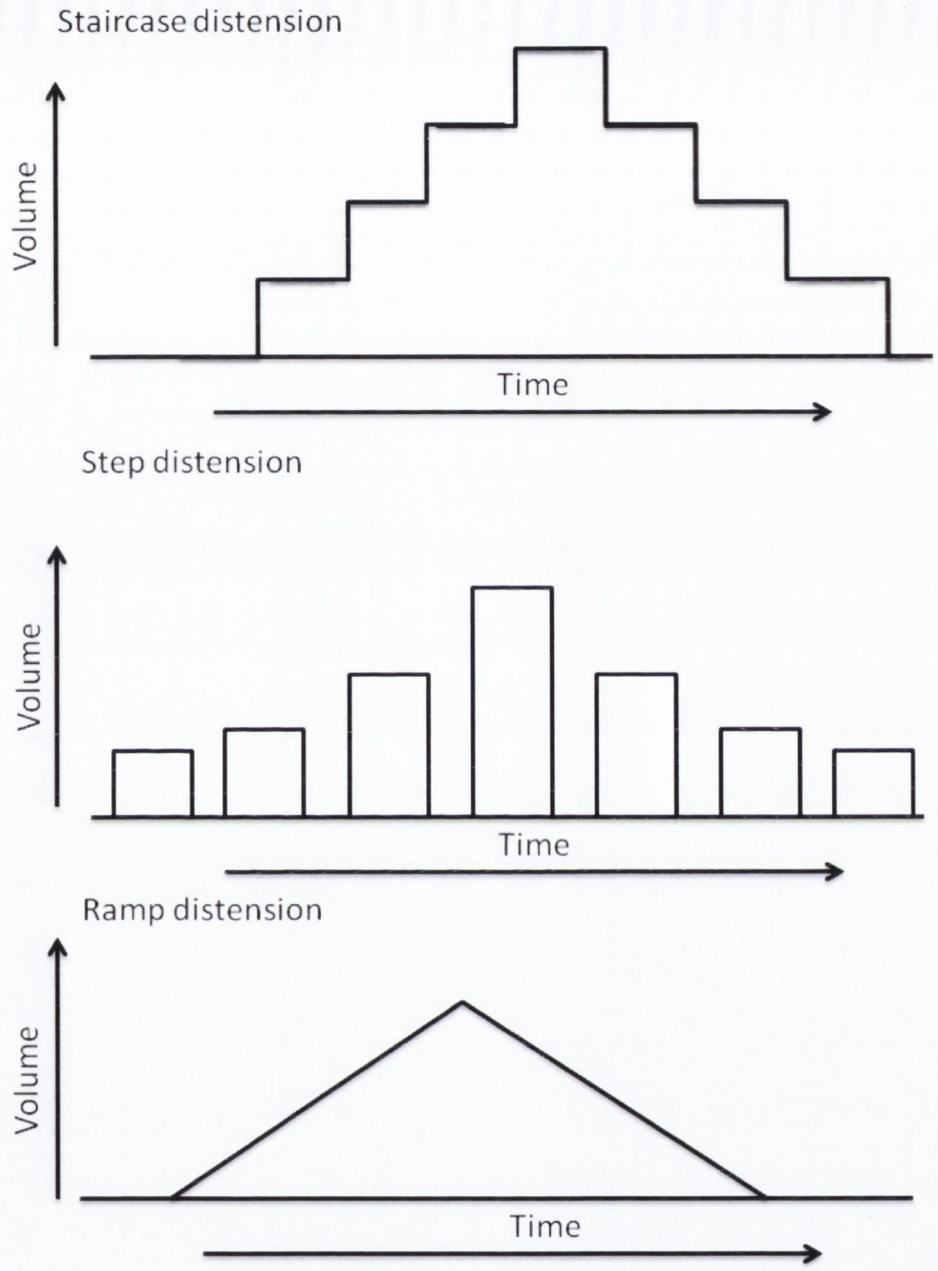

Figure 2.3 Types of Balloon Distensions

2.1.5. Evaluating Sphincter Distensibility Data

To date, methods to analyse and present sphincter distensibility based on EndoFLIP® data vary across research studies (19, 33, 34). Typically, sphincter distensibility is determined by plotting IBP (x-axis) against CSA (y-axis) during a balloon distension (CSA v pressure). The narrowest CSA

and corresponding IBP can be expressed as the distensibility index at each balloon volume. Alternatively, CSA and pressure changes can be plotted at specific balloon volumes throughout the ramp distension. The latter option allows changes in both CSA and pressure parameters to be determined between specific balloon volumes. The relationship between the two measures can also be easily viewed with this approach and hence ramp distensions been selected for use in this research study.

2.1.6. Potential Sources of Error with EndoFLIP®

As with most diagnostic tests, potential sources of error need to be examined during the development and validation of new evaluation techniques (32). This is particularly relevant when an evaluation is being adapted for use in a new anatomical region. Research involving diagnostic techniques should focus on the potential for such errors and how best to reduce them within research studies (35). This is done by establishing the accuracy or the precision of measurements obtained by the evaluation. The accuracy of a measure can be difficult to test (as a true value is often unobtainable), hence experimental error studies often focus on the precision, or reproducibility, of measures acquired from a measurement system.

Regarding EndoFLIP®, a number of factors may cause luminal measurements to be irreproducible (35). Firstly, EndoFLIP® CSA measurements are accurate even when a lumen is not circular. However, when converting CSA measures to estimated diameter measurements, FLIP assumes that the lumen is circular. Estimated diameter measurements obtained may therefore be imprecise. Additionally, the fluid dynamic consequences of a non-circular geometry need to be considered as a potential source of error as the pattern of electrode flow is going to vary. This issue is of importance to the researcher as the upper oesophageal sphincter, which will be introduced in Chapter 2.2, has a slit like configuration and an asymmetrical pressure profile. Previous publications have already addressed the effects of radial asymmetry on impedance planimetry and, to a lesser extent, FLIP measurements (17, 36). Other potential sources of error which may affect the accuracy of EndoFLIP®

measurements include the possible deviation of the catheter from the central longitudinal axis within the balloon and the slope of the luminal wall (32). A sudden change in wall diameter may not be captured by EndoFLIP® as measurements are made 5mm apart.

To date, just one study has been found by the researcher which addresses accuracy of EndoFLIP® diameter measurements (37). Using EndoFLIP® balloon catheters, authors completed bench tests at two different temperatures (23 and 37°C) using calibrated rigid cylinders with diameters varying between 5 and 26mm. The median difference between measured and actual diameter was just 0.1mm (IQR -0.25 to 0.5) or 0.88% (IQR -2.38% to 3.44%), indicating that the EndoFLIP® can produce accurate diameter measures in the range of 5 to 25mm (37). When establishing the role of EndoFLIP® in evaluating new anatomical lumens with different anatomical shapes, further accuracy studies should be completed to rule out the potential sources of error described here.

2.1.7. Clinical Utility of EndoFLIP®

Since EndoFLIP® was initially designed and successfully trialled, it has provided clinically useful information regarding the profile of the OGJ in adult healthy volunteers and in patients with GORD and achalasia (18). It has also been utilised to determine the success of fundoplication surgery in the treatment of GORD (38, 39). Recently, EndoFLIP® has been used intra-operatively by surgeons to monitor the effectiveness of a OGJ myotomy and fundoplication surgeries (40, 41). Three dimensional reconstructions of the OGJ obtained before and after these procedures visualise geometric changes in the sphincter and establish change in compliance post surgery. This valuable information can aid patient selection for various procedures and also better determine success of intervention during a surgical procedure. EndoFLIP® has since been used to measure distensibility in other anatomical lumens including the upper oesophagus in patients with oesinophilic oesophagitis, the ano-rectal region, the sphincter of Oddi and gastric bands in bariatric surgery (19, 20).

2.1.8. Diagnostic Accuracy of EndoFLIP®

As EndoFLIP® is a relatively new measurement tool, few studies have been conducted to measure its diagnostic accuracy against a robust reference standard. However, one study was found where EndoFLIP® measures of OGJ compliance were compared to reference standard oesophageal tests (41). In this animal study, two types of endoluminal fundoplication (ELF) procedures and a sham treatment were completed in a small cohort of dogs (n=14) at baseline, immediately post ELF procedure and two weeks post procedure. EndoFLIP® measures of OGJ compliance were compared to HRM, 48 hour pH monitoring (wireless Bravo pH system) and endoscopy findings. In this study, EndoFLIP® CSA measures correlated well with manometric measures of OGJ pressure ($r=-0.50$; $p<0.001$). There was a statistically significant correlation between EndoFLIP® CSA measures and cardia circumference measures based on endoscopy findings ($r=0.37$; $p=0.008$). However, no correlation was observed between EndoFLIP® CSA measures and De Meester scores obtained from pH testing ($r=0.12$; $p=0.22$)(41). The need for diagnostic accuracy studies to validate OGJ findings from EndoFLIP® in human subjects is evident. However, findings from this initial animal study are promising and demonstrate the need to use a combination of reference standard tests when determining the diagnostic accuracy of new diagnostic methods.

2.1.9. Summary

EndoFLIP® is a non-radiological measurement tool capable of providing quantitative data regarding sphincter function in a simple and timesaving procedure at the bedside. As a result of its success, this evaluation has since been used internationally to evaluate lumens at various anatomical sites beyond the OGJ. However, EndoFLIP® has not yet been used to evaluate the UOS. This is despite the fact that the UOS is poorly understood and its evaluation challenges clinicians internationally in dysphagia practice. In the next section of this chapter, the UOS will be reviewed.

CHAPTER 2.2. THE UPPER OESOPHAGEAL SPHINCTER

2.2.1. Definition

The UOS (also termed the pharyngo-oesophageal segment or POS) is an area within the upper digestive tract that forms a barrier between the pharynx and the cervical oesophagus (42). In this thesis, the term UOS will be employed rather than POS, solely because the former term is more commonly employed in the Republic of Ireland and in European research. Based on manometric studies, the length of the UOS ranges from 2 to 5 cm. The UOS is located one centimetre below the level of the vocal cords, adjacent to the fifth and sixth cervical vertebrae (43).

2.2.2. UOS Anatomy

Three muscles contribute to form the UOS; the cricopharyngeus (CP) muscle, the most inferior muscle fibres of the inferior pharyngeal constrictor (IPC) muscle and the most superior portion of the longitudinal oesophageal muscular fibres (44-46) (see Figure 2.4). The CP and UOS are therefore not interchangeable terms. In contrast to smooth muscle in the lower oesophagus and OGJ, the three muscles forming the UOS are striated.

(a) Cricopharyngeus

First described by Valsalva in 1717, the CP is the main component of the UOS. It is a C-shaped striated muscle which attaches to the dorso-lateral aspect of the lower part of the cricoid cartilage and forms a sling around the wall of the superior aspect of the cervical oesophagus (47). The closed sphincter is therefore like a horizontal band with a slit-like configuration. The cricoid lamina is anterior with the CP making up the lateral and posterior walls. The CP is bordered superiorly by the inferior pharyngeal constrictor muscle and merges inferiorly with the muscular layers of the cervical oesophagus (Figure 2.4). The slit-like configuration of the UOS has implications in terms of an asymmetric pressure profile on manometric evaluation. It may also have bearing on accuracy of diameter or CSA measurements derived from balloon distension evaluations such as EndoFLIP® (see Chapter 2.1.6).

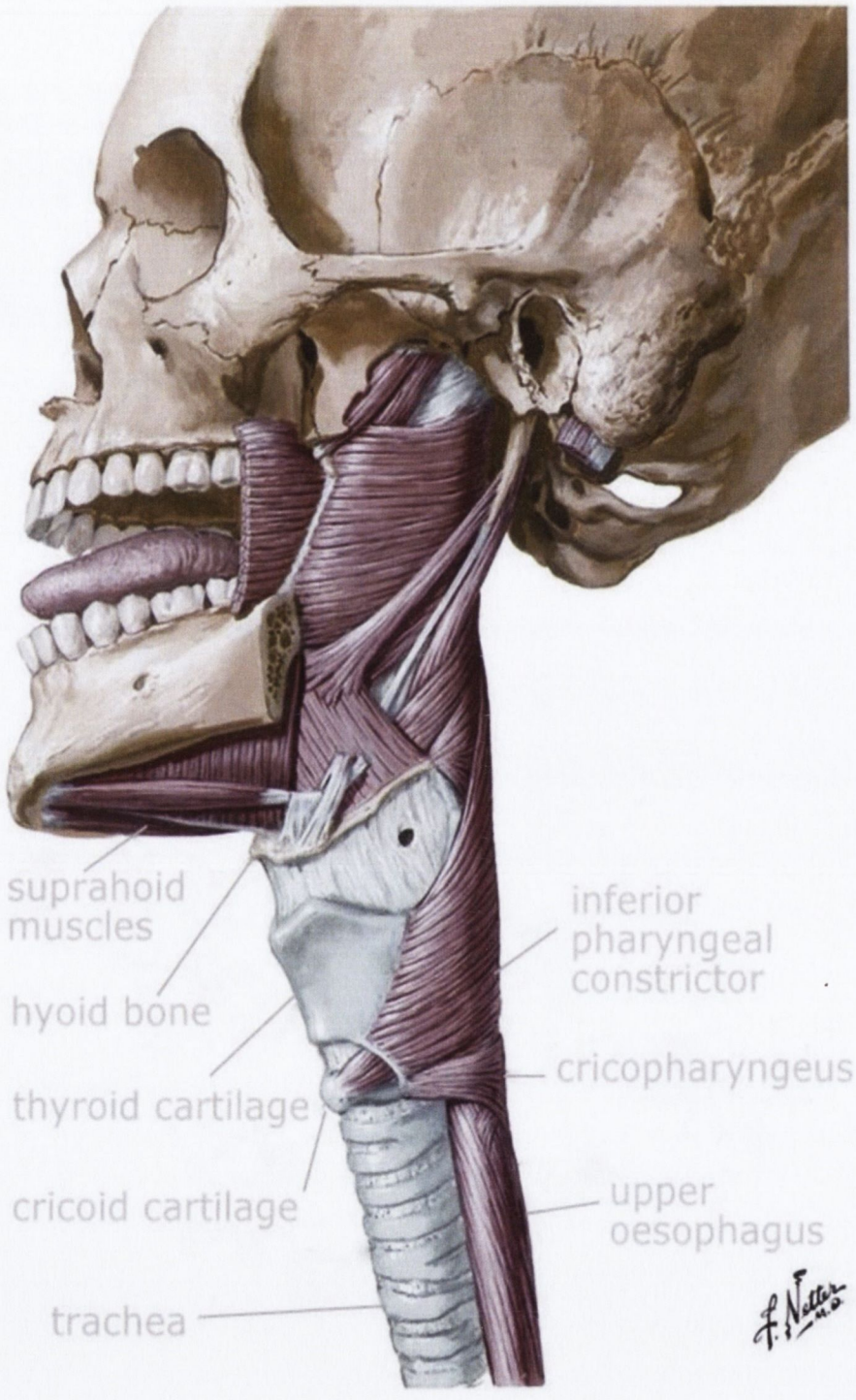

Figure 2.4 Muscular Components of the UOS (image used with permission from Elsevier)

The CP muscle is unique both in its actions and in its anatomy and physiology (48). Its horizontal (pars fundiformis) and oblique (pars oblique) muscle fibres have small average diameters (25-35 μm) which are not orientated in a parallel fashion (49). CP muscle fibres are both slow (Type I) and fast-twitch (Type II) fibres, although the former predominate (47, 50).

The CP is a bilateral muscle with bilateral innervations. The precise neural control of the CP has been difficult to determine due to differences between animal and human physiology, complexity of branching nerves and misinterpretation of EMG traces (51). Nonetheless, the recurrent laryngeal nerve from below and the pharyngeal plexus from above have been identified as neural connections (52). The pharyngeal plexus is supplied by the pharyngeal branch of the vagus nerve, the superior laryngeal nerve and the glossopharyngeal nerve. Changes in electromyographic (EMG) tracings during electrical stimulation suggest that the recurrent laryngeal nerve appears to provide the major motor innervation to the CP (53). Sensation may be provided by both the glossopharyngeal nerve and the superior laryngeal nerve (54).

(b) Inferior Pharyngeal Constrictor

IPC fibres arise from the sides of the cricoid and thyroid cartilages and spread dorsally and medially towards the median raphe (a seam-like line or ridge) posteriorly (Figure 2.4). The rostral and caudal components of the IPC, which contain varying amounts of muscle fibre types, suggest that the IPC has two functions: the slower tone generating caudal half and the rapid contraction rostral half (48).

(c) Cervical Oesophagus

The muscle fibres in the most proximal cervical oesophagus (CO) (1- 5cm) differ from the rest of the oesophagus as they are striated and arranged in a horizontal fashion (55). The cervical oesophagus is innervated by the recurrent laryngeal nerve (52).

2.2.3. Basal UOS Tone

The primary function of the UOS is maintenance of basal tone. This prevents diversion of air into the oesophagus during inspiration and phonation (aerophagia) and protects the pharynx and trachea from any retrograde passage of material refluxed from the oesophagus or stomach into the pharynx or larynx (aspiration). Presence of both types of muscle fibres (i.e., Type I slow-twitch and type II fast-twitch) enables the UOS to maintain a constant basal tone and yet relax rapidly for swallowing, belching and vomiting events (47).

All three UOS muscles help to maintain resting tone (42). The CP accounts for the distal one-third of the UOS high-pressure zone. This muscle contains more elastic tissue than most striated muscles, and the optimum length at which the CP reaches maximum active tension is 1.7 times its basal length (56, 57). Although peak intra-luminal UOS pressure is found at the caudal edge of the IPC, this may be due to higher passive forces or lower compliance of the IPC rather than stronger contraction of the IPC muscle (48). Subsequently, the CP continues to be regarded as the main muscle contributing the UOS. Resting tone in the CO has inconsistently been reported to contribute to UOS pressure.

Basal UOS tone can be altered in a variety of clinical conditions. Low UOS tone (as observed in myasthenia gravis when the neurotransmitter acetylecholine is lacking at the neuromuscular junction) can predispose an individual to regurgitation of oesophageal or gastric contents into the pharynx and trachea post swallow. High UOS tone (frequently encountered in brainstem stroke and in post-radiation fibrosis) can limit passive stretching of the UOS and hence impair UOS opening during swallowing. Evaluation of basal UOS tone is therefore a key focus in this research study. Current methods of evaluating this tone are delineated in Chapter 2.5.

2.2.4. Factors Influencing Resting UOS Pressure

Currently, the majority of studies evaluating UOS tone rely on manometric evaluations. However, resting UOS pressures based on manometric evaluations vary widely in humans (35 to 200 mmHg) (58, 59). Basal UOS tone depends on level of activity of the motor neurons, which are influenced by input from afferent and cortical pathways. As a result, UOS basal tone falls during sleep and anaesthesia (60, 61). UOS pressure increases with waking, acute emotional stress and other emotional states (62, 63). This highlights the importance of a habituation period in UOS evaluation protocols. UOS pressure also increases transiently during speech, inspiration, with movement of a catheter through the UOS, with pressure or water stimulation and with stimulation of the larynx with air puffs (64). Finally, UOS pressure and length has been found to be reduced in infants and the elderly (43, 65-67). The issue of age therefore needs to be considered in the assimilation of UOS normative evaluation data.

Of note, there is axial asymmetry within the UOS high pressure zone, with a sharp increase and gradual decrease in pressure moving inferiorly through the zone (68). A marked radial asymmetry is also observed with the pressure in the anterior-posterior plane three times that of the lateral plane (60). VFS cannot access this radial asymmetry and positioning of traditional PM probe sensors is of critical importance in clinical practice and sensor positioning can impact on manometric evaluation of UOS tone. This axial asymmetry within the UOS may also prove problematic in terms of EndoFLIP® evaluation as the CSA measurements and three-dimensional image of the lumen provided by EndoFLIP® will not capture the increase in pressure inferiorly.

2.2.5. UOS Opening During Swallowing

While the UOS is normally in a tonic state of contraction, it opens intermittently to allow trans-sphincteric flow of fluid or gas during orthograde events such as swallowing, or antegrade events such as emesis (vomiting) and eructation (belching) (69). The specific nature of UOS opening varies across each of these physiological events (69). UOS opening has a critical role in safe and efficient swallowing of food, fluids and saliva.

During swallowing, the UOS needs to open promptly and adequately to allow material to pass safely and efficiently from the pharynx into the oesophagus. This is especially critical due to the close proximity between the UOS and the airway entrance. UOS opening involves CP muscle relaxation, hyo-laryngeal displacement and pharyngeal contraction. Based on a concurrent manofluoroscopic analysis in a cohort of fifteen healthy young adult male volunteers, Cook and colleagues described five distinct phases of UOS opening which are reviewed below (Figure 2.5) (44, 70).

1. In the initial *relaxation* phase, vagal inhibition of the tonic contraction of the CP muscle occurs, as observed by needle EMG. This drop in CP pressure occurs 200 milliseconds before radiographic evidence of UOS opening and lasts 300 to 600 milliseconds (44).

2. In the second phase, passive UOS *opening* occurs via the biomechanics of hyo-laryngeal excursion. Suprahyoid muscles include the geniohyoid, mylohyoid, stylohyoid, hyoglossus and the anterior belly of digastric muscle, which are innervated by the trigeminal, facial and hypoglossal nerves (71). These suprahyoid muscles arise from various structures superior to the hyoid bone and insert into superior part of the hyoid bone (Figure 2.4). Infrahyoid muscles (including the thyrohyoid muscle which is innervated by the hypoglossal nerve) connect the hyoid bone to the thyroid cartilage. Suprahyoid and infrahyoid muscle contraction pulls the hyoid bone and laryngeal complex in an anterior and superior direction during swallowing. Current normative data regarding the degree of hyo-

laryngeal excursion during swallowing in healthy adults varies markedly across studies (72-74). As the UOS is connected to the hyo-laryngeal complex via CP attachment to the cricoid cartilage, the anterior portion of the relaxed UOS is pulled open upon suprahyoid and infrahyoid muscle contraction. The UOS assumes an oval cross section and is raised 2 to 2.5 cm in an oral direction. The geniohyoid muscle has the greatest influence on the anterior movement of the hyoid bone during swallowing, which is said to pull the UOS open (71, 72). The mylohyoid is considered to pull the hyoid bone superiorly, which protects the laryngeal vestibule during swallowing(71). Notably, the UOS can open with hyo-laryngeal excursion alone, but CP relaxation in isolation has not been observed to open the UOS. This suggests that traction forces applied by hyo-laryngeal excursion have a bigger influence on UOS opening than CP muscle relaxation.

3. In the third phase, the weight and volume of the onrushing bolus *distends* the lumen of the UOS. During this phase, the bolus is propelled by lingual and pharyngeal peristalsis through the hypopharynx and the stretched open UOS and into the cervical oesophagus.

4. The UOS *collapses* in the fourth phase after the bolus has passed through the sphincter into the oesophagus.

5. Finally, in the fifth phase the UOS *closes* as the CP actively contracts. Interestingly, anterior traction of the UOS via contraction of suprahyoid muscles can decrease intra-luminal pressure even in the absence of CP tone inhibition (64). Similarly, the UOS can relax without opening. The terms UOS relaxation and UOS opening are therefore not synonymous.

Figure 2.5 Five Stages of UOS Opening during Swallowing(44)

The ability to identify impairment at each phase of UOS opening is of paramount importance to clinicians working with dysphagia. In clinical practice, where access to instrumental evaluations and in particular to manofluoroscopy and needle EMG is limited, identification of each phase of UOS opening is a major challenge for dysphagia clinicians. This has significant implications in terms of the selection and provision of appropriate and safe dysphagia management. The lack of a valid and reliable assessment tool to provide this information was a key impetus for this research study. Additional factors influence UOS opening and hence must be considered in the development of any new assessment technique.

2.2.6. Factors Affecting Extent and Duration of UOS Opening

Factors influencing extent and duration of UOS opening in healthy adults include age, gender, bolus volume and bolus consistency. These factors therefore need to be incorporated into study protocols and their effects investigated in the evaluation of UOS opening (see Chapters 3.3, 5.3.1.1 & 5.3.3.3).

2.2.6.1. Age & Gender

Kurosu & Logemann (2009) determined that mean duration of UOS opening varies from 0.504-0.568 seconds across age groups based on VFS studies, with significantly longer opening times in older (i.e., >60 years) versus younger (20-50 years) adults (75). This change with age is in keeping with previous research and has been associated with slowing of neural processing time with age (76-78). In dysphagia research, investigators typically examine young healthy adults to acquire normative data before evaluating the effects of age on swallowing (78, 79).

Gender has also been found to affect duration of UOS opening, with slightly longer opening times (0.542 seconds versus 0.503 seconds) in females (75, 80). This gender difference in UOS opening during swallowing is therefore an important consideration in the development of new evaluation methods.

2.2.6.2. Bolus Volume & Consistency

Duration of UOS opening has also been found to be longer with larger bolus volumes (81-83). Increased bolus consistency can also enhance and prolong UOS opening during swallowing (84). The addition of barium to liquid bolus being swallowed during VFS may alter bolus consistency. Manometric studies have also established effects of age, gender, bolus size and consistency on UOS pressure, duration and onset measurements (85). New evaluation methods must also examine the effect of bolus volume on UOS opening during swallowing and demonstrate sensitivity to change in bolus volumes being swallowed.

Given the fact the variables above have been found to have a marked influence on the timing, duration and extent of UOS opening during swallowing, each of these factors need to be carefully standardised within research protocols and their effects on swallow outcomes analysed. In this research, bolus volume and gender will be carefully considered when designing study protocols and analysing data. Additionally, subjects recruited in this research will be non-elderly (i.e., 20-50 years) healthy adults to ensure the effects of age do not alter normative data. The availability of normative data pertaining to normal UOS opening helps to direct our understanding of abnormal or disrupted function.

Disorders of UOS function will be considered in Chapter 2.3.

CHAPTER 2.3. UOS DISORDERS

Unlike other areas of the gastrointestinal (GI) tract such as the gastro-oesophageal junction (OGJ), clinicians and researchers are only beginning to understand UOS function and dysfunction due, in part, to limitations in evaluation techniques. It is known that impaired UOS opening can result from disordered neurally-mediated relaxation of the UOS, suboptimal hyo-laryngeal excursion, CP fibrosis, weak bolus propulsion and frequently it is a combination of these factors (86).

2.3.1. Disordered CP Relaxation

Failure of the CP to relax for at least 200 milliseconds prior to the onset of UOS opening is a motor disorder stemming from the rostral medulla (87). No studies have been found which identify the effects of ageing on duration of CP relaxation during swallowing. Any conditions affecting the rostral medulla may present with impaired CP relaxation. When the CP does not relax prior to UOS opening, it cannot be stretched open as easily upon hyo-laryngeal excursion. This phenomenon cannot be observed during VFS and currently can only be diagnosed from a combined manofluoroscopy study or, more accurately, from needle EMG of the CP muscle segment. However, neither of these evaluations are readily accessible in clinical practice (88). A new evaluation of CP relaxation would be of significant benefit to UOS evaluation.

Williams, Wallace, Ali and Cook (2002) reviewed 396 manofluoroscopic studies of patients with pharyngeal dysphagia over a nine year period (89). They found that only 4.8% of patients (n=18) evaluated had a confirmed failure of CP relaxation, which suggests that this is a rare presentation. Medullary lesions or Parkinson's Disease (PD) made up ninety percent of failed CP relaxation cases in their study (89). While this was a retrospective review of these patients, with varying reasons for referral for manofluoroscopy, these findings are in keeping with other studies. Wallenberg's syndrome (lateral medullary infarction) has been cited as a frequent cause, while 25% of people with PD have been found to have failed UOS relaxation (90).

Interestingly, failed CP relaxation can be observed in individuals with PD before the clinical onset of dysphagia (90). This suggests that subsequent phases of UOS opening (i.e., hyo-laryngeal excursion or pharyngeal propulsion) may, in some cases, be able to compensate for impaired CP relaxation to some degree. While failed CP relaxation has not, in isolation, been associated with any specific symptom of pharyngeal dysphagia, its presence provides evidence of medullary disease (86). Other acute and progressive neuromyogenic groups observed to have failed CP relaxation include other extrapyramidal disorders (e.g., Huntington's disease), motor neurone disease, syringobulbia, brainstem tumour and brainstem compression secondary to cerebral haemorrhage (89).

2.3.2. Weak Hyo-Laryngeal Excursion

The role of hyo-laryngeal excursion in UOS opening is already discussed in Chapter 2.2.5 (Figure 2.5). Any alteration in the timing, extent and duration of hyo-laryngeal excursion during swallowing can affect safe and effective bolus passage through the UOS. Individuals with dysphagia have been shown to have less hyoid bone displacement both anteriorly and superiorly than normal subjects (91). This limits UOS opening during swallowing and has been associated with aspiration (92). In fact, individuals with reduced hyoid excursion have been found to have 3.7 times greater risk of aspiration (93). Establishing the presence of impaired hyo-laryngeal excursion is complicated in clinical practice by a marked variety of normal ranges across VFS studies (73).

Impaired hyo-laryngeal excursion is commonly caused by the underlying neuromuscular disease in dysphagic populations (e.g., motor neurone disease, stroke and Parkinson's disease). Any impairment to trigeminal, facial or hypoglossal nerve function can lead to impaired contraction of the suprahyoid and thyrohyoid muscles. This prevents adequate traction of the relaxed CP muscle via the hyo-laryngeal complex and results in inadequate UOS opening for complete bolus clearance.

Another frequent cause of impaired hyo-laryngeal excursion is radiation-induced muscle fibrosis and scarring in individuals with head and neck

cancer (94). Muscles involved in UOS opening (i.e., CP, IPC, suprahyoid and thyrohyoid muscles) which are exposed to radiation treatment may become more rigid and less supple, impacting markedly on range of motion. This may occur as late as twenty years after treatment (95). While the incidence of head and neck cancer continues to increase with subsequent high dose radiation, it is anticipated that new advances, such as dose intensity-modulated radiation therapy (IMRT), can spare surrounding tissue and hence minimise complications of radiation treatment (96).

2.3.3. Poor Bolus Propulsion

Altered UOS opening can also be a manifestation of weak pharyngeal propulsion. During swallowing, the hypopharynx must compress and shorten to direct a bolus towards the UOS. If pharyngeal constriction is weak, intra-pharyngeal forces imparted by the advancing bolus may not be sufficient to maximise UOS opening. Loss of propulsive force from pharyngeal constrictor muscles is considered to be more important than UOS relaxation in terms of dysphagia severity.

There are a number of conditions associated with disordered UOS opening. These are considered in the next section.

2.3.4. Conditions Associated with UOS Dysfunction

Conditions affecting any of the five phases of UOS opening (Figure 2.5) can lead to oro-pharyngeal dysphagia. Specific diagnostic groups associated with impaired UOS opening are tabulated below (Table 2.1). In many of these conditions (e.g., inclusion body myositis), identification of impaired UOS opening can aid in the diagnosis of these conditions (97). The heterogeneity of diagnostic groups requires that new evaluation methods be tested within specific clinical groups. In Chapter 2.3.5, one diagnostic group with known UOS dysfunction is examined in more detail.

Table 2.1 Conditions Associated with UOS Dysfunction

Neurological Conditions	Gastroenterological or Carcinoma related Conditions	Systemic Conditions	Structural or Surgical Conditions
• Stroke • Parkinson's Disease (PD) • Motor Neurone Disease • Myasthenia Gravis • Inflammatory myopathies (inclusion body myositis, polymyositis, dermato-myositis) • Huntington's disease • Brainstem tumour • Muscular dystrophies • Spino-cerebellar degeneration	• GORD • Globus pharyngeus • Pharyngitis • Benign oesophageal tumour • Head and neck cancer inc. partial or total laryngectomy • Oesophageal cancer • Radiation therapy	• Diabetes • Scleroderma • Botulism • Hyper-thyroidism • Myxoedema (severe hypo-thyroidism) • Rabies • Lead poisoning • Diphtheria • Syringobulbia • Poliomyelitis	• Zenker's divertic-ulum • Stricture • Post-surgical • Foreign body • Trauma

2.3.5. Total Laryngectomy

A total laryngectomy is completed as a primary or secondary treatment for laryngeal carcinoma. Surgery involves removal of the entire larynx and separation of the airway from the oesophagus. A permanent tracheostoma is created in the anterior neck for breathing; hence individuals lose the ability to voice conventionally and experience changes in taste, smell and swallowing (Figure 2.6). Major structural changes result from the removal or "skeletonisation" of the entire larynx. The hyoid bone, true and false vocal cords, epiglottis, cricoid cartilage and two or three tracheal rings are removed during surgery. Depending on the severity and spread of disease, surgery may also include total or partial pharyngectomy, oesophagectomy or neck dissection.

After laryngectomy surgery, a new reconstructed pharyngeal tract (termed a neopharynx) remains. According to CT and sonographic studies, the neopharynx is typically round or ovoid in shape and connects the base of tongue to the cervical oesophagus (98). Preserved inferior pharyngeal constrictor and cricopharyngeus muscles are repositioned and resutured to form a level of closure over the repaired pharynx. This appears on VFS as a narrow region and is called the pharyngo-oesophageal segment (POS). In this thesis, the reconstructed UOS in individuals with total laryngectomy will hereon in be referred to as the POS (Figure 2.7). The POS replaces what was previously the UOS. Of importance, the ability of this POS region to dilate influences the individual's ability to swallow various food consistencies.

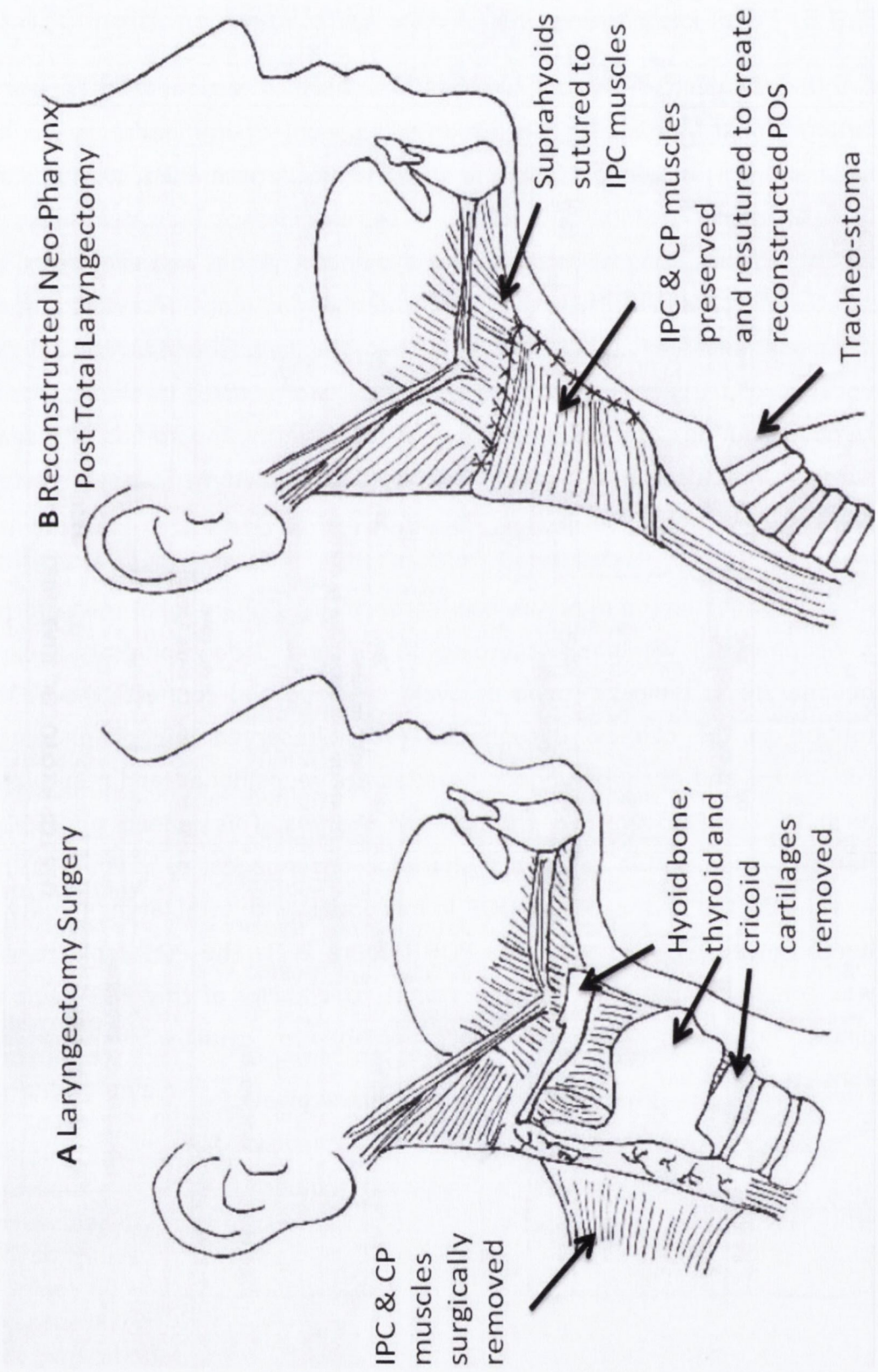

Figure 2.6 Structural Changes post Total Laryngectomy

2.3.6. Importance of Evaluating the POS Region in Individuals with Total Laryngectomy

Dysphagia post total laryngectomy has multiple causes including anatomical and physiological alterations, sensory changes (smell and taste) and side-effects of radiation and/or chemotherapy. In a recent study, 72% of people with total laryngectomy self-reported symptoms of dysphagia (99). Aspiration is typically not an issue due to separation of the pharynx and the airway, although it can present if patients develop a fistula. Instead, pharyngeal bolus clearance is frequently impaired post total laryngectomy with marked pharyngeal residue or regurgitation observed on VFS and reduced pharyngeal pressure seen on PM (100). This impaired bolus clearance may be explained by limited driving forces of the tongue base and reduced pharyngeal contraction post surgery. Reduced stripping action of the posterior pharyngeal wall limits bolus propulsion during swallowing. In addition, absence of the hyoid bone and resection of the suprahyoid muscles during surgery results in the absence of hyo-laryngeal excursion during swallowing which facilitated bolus clearance. However, reattached suprahyoid muscles contract during swallowing and pull on the reconstructed segment to facilitate POS opening.

The tone within the POS region may differ considerably from the pre-surgical UOS in individuals post total laryngectomy. Reduced tone in this region can be caused by the absence of the cricoid cartilage anteriorly, where the CP muscle attached bilaterally pre-operatively. Surgical resection and subsequent reconnection of the IPC and CP muscles must also alter tone. An adjunct myotomy (cutting of individual muscle fibres) of the CP muscle, often performed during laryngectomy surgery to aid speech production, can also markedly reduce POS tone (101). In contrast, high POS tone can result from a stricture or spasm post-surgery which inhibits air flow and hence speech production. Radiation can also induce fibrosis of the POS musculature which can increase POS tone and opening efficiency during swallowing. POS tone can subsequently alter significantly post laryngectomy surgery (102, 103). The consequence of this altered tone can

have a marked impact on swallowing and speech efficiency. To date, these alterations have been studied most frequently using VFS and PM.

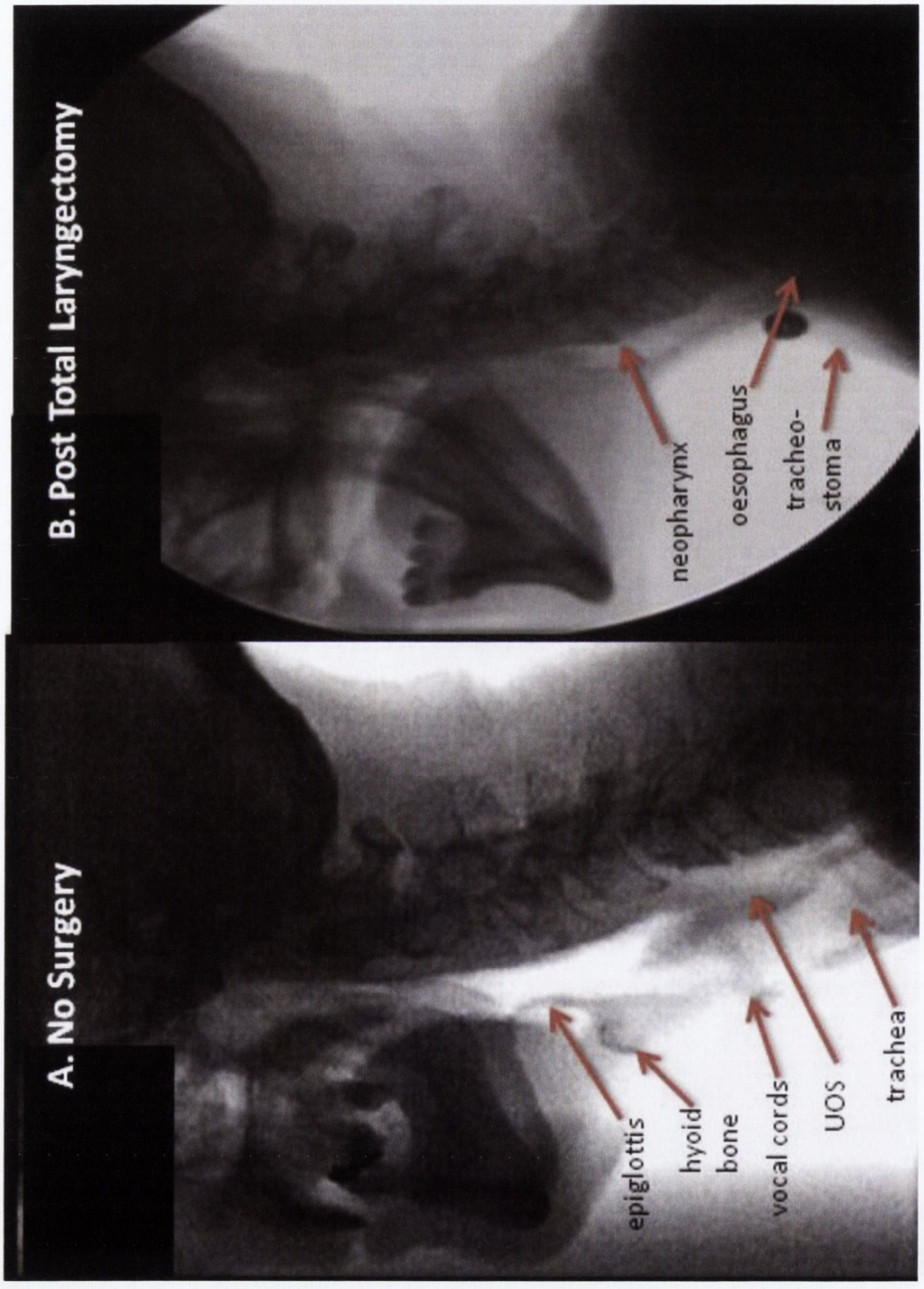

Figure 2.7 Anatomical Changes post Total Laryngectomy on Videofluoroscopy

2.3.7. Rationale for Selecting Individuals with Total Laryngectomy for Clinical Studies

The homogeneity of a total laryngectomy group contrasts markedly with other diagnostic groups such as stroke and PD. In both of these neurological groups, causes and features of dysphagia and UOS dysfunction can be heterogeneous in nature (i.e., poor hyo-laryngeal excursion, disordered CP relaxation or weak bolus propulsion) and typically present alongside several other co-morbidities which may complicate a preliminary evaluation process. Additionally, within the total laryngectomy population there is typically a lack of cognitive changes as well as the fact that total laryngectomy populations frequently have probes inserted trans-nasally as part of outpatient clinic appointments in order to examine the laryngeal region. For these reasons, individuals with total laryngectomy are an ideal group for preliminary clinical studies.

In Chapter 2.4, management strategies employed to target disordered UOS opening in clinical practice are reviewed.

CHAPTER 2.4. CLINICAL MANAGEMENT OF IMPAIRED UOS OPENING

2.4.1. Introduction to Management Approaches

The UOS can be modified with rehabilitation or surgery and has, therefore, caught the international attention of dysphagia clinicians and surgeons. While more traditional methods to manage dysphagia (diet modification and tube feeding) are still in routine use, they are generally combined with more modern dysphagia interventions targeting impaired UOS opening during swallowing. These interventions can be grouped into compensatory, rehabilitative, pharmacological and surgical categories. Generally speaking, a step-up approach to UOS management is employed, where the effects of conservative intervention (i.e., compensation or rehabilitation) are initially observed before considering more invasive treatment (Tx) (see Figure 2.8). For this reason, accurate measurement of the extent and duration of UOS opening during swallowing is paramount throughout the course of dysphagia rehabilitation. While VFS and PM provide useful information on UOS opening during swallowing, clinicians currently struggle to ascertain objective change in UOS function. The majority of health care settings remain reluctant to complete invasive dysphagia interventions until candidacy criteria become less subjective and until intervention protocols become more consistent. New quantitative data on UOS function to complement existing diagnostic evaluations is urgently required in clinical practice to advance clinical dysphagia management.

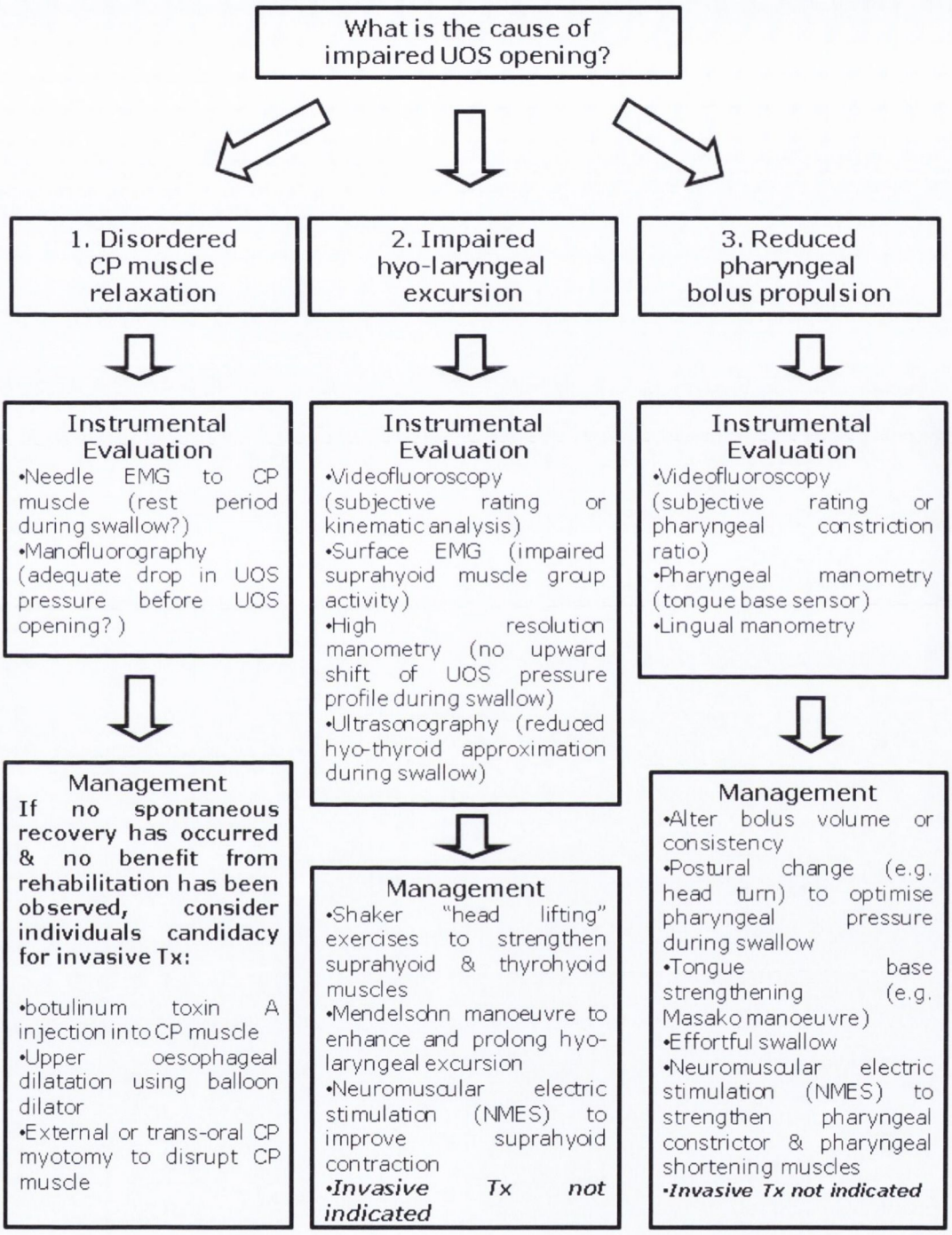

Figure 2.8 Management of Impaired UOS Opening in Clinical Practice[3]

[3] Tx= treatment

2.4.2. Compensatory Postures and Manoeuvres

In order to compensate for impaired UOS opening during swallowing, voluntary postures or manoeuvres can be employed by individuals with dysphagia in clinical practice. These postures or manoeuvres are purported to modify the geometry of the upper aero-digestive tract and hence induce short-term changes to the dynamics of the oro-pharynx. Strategies are selected to minimise aspiration and facilitate bolus clearance during swallowing. They provide an immediate but typically transient effect on the efficiency or safety of swallowing, and hence they need to be employed for every swallow. The specific posture or manoeuvre employed is dependent on the nature of the swallow impairment observed during an objective dysphagia evaluation.

2.4.2.1. Postural Strategies

Pioneered by Larsen in the early 1970s, "neck-flexed postures" were first introduced to reduce the risk of aspiration and improve deglutition (104). When employed, chin tuck, head back, head turn or rotation and side-lying postures affect the direction of bolus flow during swallowing and change the physical dimensions of the pharynx (Figure 2.9). Postural strategies typically provide an immediate but transient effect on safety (i.e., prevention or reduction of aspiration) and/or efficiency (i.e., prevention or reduction in pyriform or vallecular residue) of swallowing. They need to be employed for all swallows and, if not executed, swallowing will return to the prior disordered status. Seventy-five percent of SLTs employ postural techniques in the management of individuals with dysphagia (105). Perhaps their frequent use is due to the lack of resources and limited training required to use them, unlike other dysphagia interventions. Nonetheless, SLTs should be cognisant of several individual factors before recommending these strategies. Individuals generally need to have preserved cognition, adequate physical reserve and good awareness of their swallowing difficulty in order to consistently comply with recommendations (106).

	Posture	Indications	Effects
Chin Tuck		Delayed pharyngeal swallow Reduced tongue base retraction Reduced airway closure	Widens valleculae Improves tongue base to posterior pharyngeal wall contact Prevents penetration into airway
Head Back		Prolonged oral transit time Weak lingual tone Impaired bolus propulsion towards pharynx	Uses gravity to clear oral cavity
Head Turn to Weak Side		Unilateral pharyngeal paresis (asymmetrical residue in pharynx	Redirects bolus away from weak side of pharynx Reduces asymmetrical residue in pyriform sinuses post swallow
Head Rotation		UOS dysfunction	Passively stretches open UOS and reduces UOS pressures Improves bolus clearance through UOS and reduces pyriform residue
Lying Down on One Side		Reduced pharyngeal contraction Residue throughout pharynx	Reduces pharyngeal residue

Figure 2.9 Postural Strategies employed in Dysphagia Research

(a) Chin Tuck

The chin tuck or chin down posture is a widely employed technique where individuals with dysphagia are instructed to tuck the chin towards the chest before the swallow is initiated (Figure 2.9). Chin tuck is indicated in patients who present with a delay in initiation of the pharyngeal swallow, reduced tongue base contraction and reduced airway entrance closure during swallowing (106). The posture is believed to widen the vallecular space, narrow the airway entrance and increase tongue base retraction towards the posterior pharyngeal wall during swallowing. The majority of studies to date (see Table 2.2), only two of which were randomised control trials, have focused on the effectiveness of chin tuck in eliminating aspiration in individuals with neurological disease and head and neck cancer (107-117). Of note, research on the effectiveness of chin tuck in eliminating aspiration has been inconsistent to date (108, 117).

Only a small number of studies have examined effects of the chin tuck on swallowing parameters beyond aspiration such as UOS opening (118). Welch et al focused on the effects of chin tuck on pharyngeal dimension during VFS (111), and Shanahan et al examined changes in timing of swallow onset with the chin tuck posture (119). Bülow et al used PM and VFS to establish the effects of chin down posture (among other interventions) on pharyngeal and UOS pressure events during swallowing in healthy volunteers and patients with pharyngeal dysphagia (120, 121). They found that chin tuck reduced pharyngeal contraction and reduced laryngo-hyoid distance in healthy adults and the posture did not prevent aspiration in patients with dysphagia (120, 121). Using HRM, McCullough et al found that chin tuck had a bigger impact on UOS pressures than on velo-pharyngeal or tongue base pressures in seven healthy volunteers (122). While duration of UOS opening was longer during chin tuck swallow in this study, this finding was statistically insignificant (122). While authors suggested that this may have been due to small numbers, only one other study was found in the literature where duration of UOS opening was increased with chin tuck posture (123) (Table 2.2).

Table 2.2 Studies Investigating Chin Tuck Posture

Study	N	Medical Diagnosis	Test	Effectiveness
(108)	579	PD & Dementia	VFS	Eliminated aspiration in 33% (92/228) PD patients & 26% (90/351) dementia patients
(124)	40	Healthy adults	PM	↑ pressure-generation duration in middle sensor UOS nadir pressures were significantly lower for effortful than non-effortful swallows
(125)	20	Healthy adults	PM	Earlier onsets and peaks of pharyngeal pressures Total pressure event durations were greater and rise times were significantly shorter
(126)	10	Healthy adults	OM	↑ peristaltic amplitudes within the distal smooth muscle region of the oesophagus
(127)	22	Healthy adults	sEMG	↑ Suprahyoid sEMG ↑ pharyngeal pressure at 2 proximal pharyngeal sensors. ↓ UOS pressure
(128)	18	Healthy adults	PM	↑ pharyngeal pressure and UOS relaxation durations pressure duration measured in the upper pharynx was significantly longer than that measured lower in the pharynx
(109)	20	PD & cerebellar ataxia	VFS	Eliminated aspiration in 7.7% (1/13) of PD patients and in 57% (4/7) ataxia patients
(114)	30	Mixed neurological	VFS	Inconsistent improvement in aspiration and premature spillage
(120)	8	Stroke, H&N cancer	VFS	Did not alter peak amplitude or duration of intra-bolus pressure
(129)	8	Stroke, H&N cancer	VFS	Did not reduce aspiration but reduced depth of penetration. Pharyngeal retention not improved. Reduced distance between pharyngeal structures.
(123)	64	Healthy adults	PM	↑oral pressures ↑ duration of maximal anterior hyoid excursion ↑ Duration of laryngeal vestibule closure ↑ duration of UOS opening. ↑ Superior hyoid bone movement. ↓oral residue (not sig)
(121)	8	Healthy adults	VFS	↓ hyoid–mandible distance pre-swallow due to an elevation of the hyoid and the larynx, which caused a significantly reduced maximal hyoid movement & significantly reduced laryngeal elevation during swallow
(119)	30	Mixed neurological	VFS	Eliminated aspiration in 50% (15/30)
(107)	84	Mixed diagnosis	VFS	Eliminated aspiration in 25% on all volumes (21/84)
(111)	30	Mixed	VFS	4/6 of postural distances/ angles significantly changed with the chin tuck position. Chin down does not always widen valleculae.
(110)	18	Mixed	VFS	50% laryngeal closure (9/18)

Other methodological limitations affect the significance of research findings regarding the chin tuck manoeuvre. Primarily, research has demonstrated huge variability in the execution of the chin tuck (130). In a survey of forty-two SLTs in Japan and USA, there was poor agreement regarding the meaning of "chin down" and "chin tuck" postures (131). A standard definition of the posture is required within and across research studies in order to derive clinical benefit from evidence-based research. Of note, the sensitivity of the non-instrumental clinical examination in detecting aspiration during the chin tuck across consistencies posture is low (132). This highlights the need to trial it during instrumental examination. Finally, of interest from a compliance and quality of life viewpoint, only 37% (70/188) of individuals with Parkinson's disease (PD) within a recent randomised control trial considered chin tuck to be an easy or pleasant intervention (108). The influence of this head posture on UOS opening must be tested in any new method to evaluate this area. This includes sensitivity of the tool to evaluate change in UOS during swallowing as well as the individual's ability to complete these postures with the assessment probe in-situ.

(b) Head turn

In individuals with unilateral pharyngeal weakness (e.g., post stroke) who present with asymmetrical pharyngeal residue post swallow on VFS or FEES, the head turn posture is thought to redirect the bolus from a weak or paretic side of the pharynx and hence the bolus flows down the stronger more functional side during swallowing (133) (see Figure 2.10). Similarly, individuals with poor UOS opening or poor vocal cord closure may benefit from the head turn as this posture is purported to passively stretch open the UOS lumen to improve bolus clearance during swallowing. Individuals with pharyngeal dysphagia using this strategy need to turn their head ninety degrees to one side before initiating every swallow. As with the chin tuck posture, cognition warrants consideration before this technique is recommended.

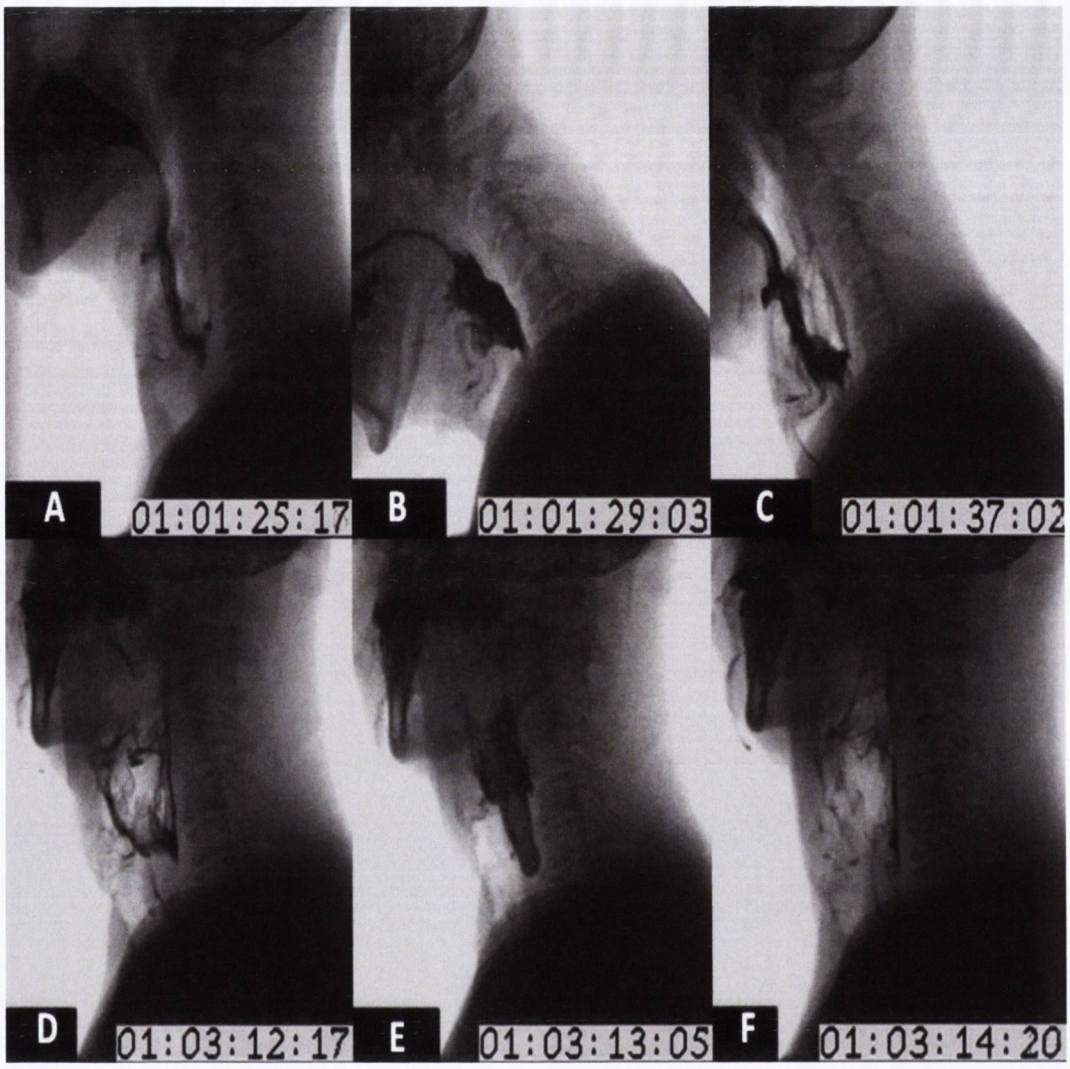

Figure 2.10 VFS Images of Head Turn Posture during Swallowing[4]

[4] VFS Images of a 53 year Old Male with Dysphagia post Stroke Completing Chin Tuck and Head Turn Postural Strategies.
In images A-C, patient completes a 10ml swallow on nectar-thick fluids using a chin tuck posture (A, B). However, aspiration into trachea and moderate pharyngeal retention is evident post swallow (C). In images D-F, this patient completes a head turn posture on the same bolus volume and consistency (E, F). There is improved bolus clearance with less residue in the pharynx post swallow and a reduction of aspiration into the trachea (F).

Despite the frequency of its use in clinical practice, the evidence for the head turn posture is restricted to a small number of exploratory studies using VFS and PM which focus mostly on healthy volunteers (Table 2.3). Initially, the effectiveness of the head turn posture was examined in five individuals post lateral medullary stroke during VFS (134). During head turn, the bolus moved away from the direction of the rotation (i.e., when individuals turned head to left side of unilateral weakness, bolus travelled down right side of pharynx) and the posture increased UOS opening and the amount of the bolus being swallowed. These benefits may have marked implications from both an oral intake and a quality of life viewpoint for patients with significant dysphagia. However, the statistical significance of these findings was not explored in this study (134). In a separate VFS study, head turn posture eliminated aspiration in just 26% (20/77) of patients with mixed diagnoses (107).

Table 2.3 Studies Investigating Head Turn Posture

Study	N	Medical Diagnosis	Test	Effectiveness
(135)	18	Healthy volunteers	HRM only	Resting UOS pressures were higher with head turn towards sensor than neutral and were lower with head turn away from sensor than neutral. Length of UOS zone is shorter with head turn away from sensor than in head neutral.
(136)	7	Healthy volunteers	HRM only	Effect on UOS pressure but not tongue base or velo-pharynx. Significant reduction in pre-swallow mean maximum UOS pressure (227-118mmHg).
(137)	7	Healthy volunteers	VFS & PM	Bolus lateralised away from the direction of head rotation. Pharyngeal peak pressures toward the side of head rotation were significantly increased. Pharyngeal pressures opposite the side of head rotation were not affected. Significant fall in UOS resting pressure and a delay in UOS closing.
(107)	77	Mixed aetiologies	VFS only	Eliminated aspiration for all volumes in 20 (26%) of 77 patients.
(134)	5	Lateral medullary stroke	VFS only	Increased AP UOS opening diameter (2mm). Reduced UOS pressure during swallow (18mmHg or 35%). Estimated amount of bolus swallowed increased from 33% to 65%.

Ohmae, Ogura, Karaho, Kitahara and Inouye (1998) studied the effects of the head turn during VFS and PM in seven healthy subjects (137). Authors found that during the head turn, the bolus lateralised away from the direction of head rotation. Peak pharyngeal pressures toward the side of head rotation were significantly increased ($p<0.05$) while pharyngeal pressures opposite the side of head rotation were not affected. A statistically significant fall in UOS resting pressure (38mmHg±3-33mmHg±4; $p<0.05$) was noted, as was a statistically insignificant delay in UOS closing with the head turn posture (0.72mmHg±0.02-0.76mmHg±0.02) (137). The effects of head turn on pharyngeal and UOS pressures have also been examined using HRM in seven healthy volunteers (122). While head turn did not affect maximum velo-pharyngeal or tongue base pressure, it significantly decreased pre-swallow maximum UOS pressures (227mmHg±100-118mmHg±60; $p=0.017$). Head turn also increased duration of UOS opening: while this increase may have been clinically significant, the increase was not statistically significant ($p=0.180$). Similar findings were made by Takasaki et al when studying changes in UOS pressure with head turn using HRM (135).

The head turn posture has been found to increase UOS opening (as measured fluoroscopically) by 2mm and reduce UOS resting pressure by 18mm Hg (35%) in adult healthy volunteers (134). The head turn also allowed the bolus to move away from the direction of the head rotation. It was determined in this study that the head turn also increased the proportion of bolus passing through the UOS and extent of UOS opening in a subgroup ($n=5$) with lateral medullary syndrome and unilateral pharyngeal weakness (134). As with the chin tuck, the head turn would seem an important postural modification to evaluate in exploring the clinical utility of any new diagnostic method.

(c) Combination of Head Postures

Rasley et al (1993) used VFS to evaluate the effectiveness of five postures (head rotation, head tilt, chin down, chin up and lying down) in 165 individuals with aspiration (107). Seventy-seven percent of participants benefited from one or more of these strategies (i.e., there was an increase

of bolus volume they could swallow without aspiration). In 25% of participants, aspiration was eliminated for all bolus volumes and during cup drinking (107).

2.4.2.2. Swallowing Manoeuvres

Swallowing manoeuvres are defined as volitional movements of the oral, pharyngeal, or laryngeal structures before or during the pharyngeal phase of the swallow that are intended to increase swallow force or alter airway protection mechanisms (138). These interventions may have temporary or permanent changes to swallow function. Manoeuvres should initially be trialled on VFS (VFS) or FEES to establish effectiveness in terms of swallow safety and efficiency. As with postures already described, manoeuvres can be difficult to execute and tend to be more appropriate for individuals with no significant cognitive involvement.

(a) Effortful Swallow

The effortful (or modified Valsalva) swallow was first introduced by Kahrilas and colleagues as a compensatory technique (139), although its role in the longer-term rehabilitation of weak pharyngeal contraction has since been purported (140). This posture is frequently attempted during instrumental examination (e.g., VFS or FEES) when residue is observed in the valleculae or on the posterior pharyngeal wall post swallow. Individuals with dysphagia are simply instructed to "squeeze hard with all of the muscles" when swallowing. By increasing effort during swallowing, both tongue base retraction and pharyngeal contraction have been found to increase (123, 128, 141-143) (Table 2.4). Other established effects of the effortful swallow include prolonged UOS opening, longer maximum anterior hyoid excursion and longer laryngeal vestibule closure (123, 124, 127, 128, 144). Its effect on peristalsis in the smooth muscle of the oesophagus has also been determined (126, 145).

Table 2.4 Studies Investigating Effortful Swallow[5]

Study	N	Diag-nosis	Test	Effectiveness
(143)	3	H&N Ca	VFS-PM	Tongue base-pharyngeal wall pressures and contact duration increased.
(120)	8	Patients	VFS-PM	Did not alter peak amplitude or duration of intra-bolus pharyngeal pressures at level of UOS.
(129)	8	Patients	VFS-PM	Did not reduce the number of misdirected swallows, but reduced the depth of contrast penetration into the larynx and trachea. No change in pharyngeal retention. Does not improve weak pharyngeal constriction.
(142)	18	Healthy adults	HRM	Maximum velo-pharyngeal, hypo-pharyngeal and UOS values during dry and water swallows were statistically higher.
(144)	80	Healthy adults	Tongue pressure & surface EMG	No difference in amplitude between younger and older subgroups. Older subgroup (60 years+) had slower rise times to peak anterior tongue-palate pressure.
(124)	40	Healthy adults	PM	Increased pressure-generation duration in middle sensor. UOS nadir pressures were significantly lower for effortful than non-effortful swallows.
(125)	20	Healthy adults	PM	Earlier onsets and peaks of pharyngeal pressures. Total pressure event durations were greater and rise times were significantly shorter.
(126)	10	Healthy adults	OM	Increased peristaltic amplitudes within the distal smooth muscle region of the oesophagus.
(127)	22	Healthy adults	PM-sEMG	Increased suprahyoid sEMG values and pharyngeal pressure at 2 proximal pharyngeal sensors. Reduced UOS pressure observed.
(128)	18	Healthy adults	PM	Increased pharyngeal pressure and UOS relaxation durations. Pressure duration measured in the upper pharynx was significantly longer than that measured lower in the pharynx.
(123)	64	Healthy adults	VFS & oral pressure	Increased oral pressure and increased duration of maximal anterior hyoid excursion, laryngeal vestibule closure and UOS opening. Increased superior hyoid bone movement Reduced oral residue (not statistically significant).
(121)	8	Healthy adults	VFS-PM	Reduced hyoid–mandibular distance pre-swallow due to an elevation of the hyoid and the larynx, which caused a significantly reduced maximal hyoid movement and a significantly reduced laryngeal elevation during swallow.

[5] H&N Ca= head and neck cancer

Unlike many other postures and manoeuvres, the biomechanical and physiological effect of the effortful swallow has been tested using a variety of instrumental evaluations (i.e., VFS; tongue, pharyngeal and oesophageal manometry (OM); HRM; surface EMG) across oral, pharyngeal and oesophageal phases of swallowing (Table 2.4). However, conflicting evidence regarding its effects on pharyngeal pressure have been found (121), with lower mean peak pressures during effortful swallowing in volunteers and patients found on manometric evaluation in two studies (121, 129). Differences in the execution of the technique have also been described, with greater increases in pharyngeal pressure when tongue-to-palate contact pressure is emphasised during swallowing (146). The influence of effortful swallowing on UOS opening should be investigated during the development of any new dysphagia diagnostic method. The sensitivity of a new tool in identifying change in UOS opening during swallowing is of prime importance.

(b) Supraglottic Swallow

The supraglottic swallow was initially designed for patients post-laryngectomy to close the airway at the true vocal cords before and during swallowing in order to protect the airway from aspiration (147, 148). As part of this manoeuvre, individuals are asked to introduce a bolus into the oral cavity and to take a deep breath and hold the breath before and during swallowing. They then cough after swallowing and before inhaling to clear any residue near the airway entrance post swallow (149). Patients not only require sufficient cognition to comply and adhere to this intervention, they also need to have a minimum respiratory reserve in order to complete the strategy routinely during meals. Perhaps for this reason, the supraglottic swallow is not recommended clinically by SLTs as frequently as other swallowing manoeuvres (105).

The majority of research on this manoeuvre to date has focused on individuals with head and neck cancer (147, 150-152) using VFS and PM evaluations (see Table 2.5). However, the efficacy of this manoeuvre has also been investigated in individuals with Parkinson's disease and cerebellar ataxia (109). Evidence suggests the supraglottic swallow can be difficult for

individuals to master (109), and it is not always effective in eliminating aspiration (114, 129, 147). Furthermore, manometric studies suggest that this manoeuvre does not alter pharyngeal pressures during swallowing (120). Candidacy for this manoeuvre should therefore be established on VFS or FEES and ideally individuals should be reviewed regularly to monitor the technique and its effectiveness. The supraglottic swallow is a key strategy in dysphagia practice. During the development of any new diagnostic tool, the effects of the supraglottic swallow on swallow parameters should be explored.

Table 2.5 Studies Investigating Supraglottic Swallow[6]

Study	N	Medical diagnosis	Test	Effectiveness
(109)	20	PD & cerebellar ataxia	VFS	1/12 (8%) patients with PD could execute manoeuvre and eliminate aspiration
(114)	30	Mixed neurological	VFS	Inconsistent reduction of premature spillage and inconsistent elimination or reduction of aspiration or penetration
(150)	23	H&N Ca (posterior tongue resection)	VFS	Did not eliminate aspiration in patients with larger resections but did in small resection group.
(120)	8	Mixed	VFS-PM	Did not alter weak pharyngeal constriction
(129)	8	Mixed	VFS-PM	Did not reduce aspiration or depth of penetration & did not improve pharyngeal retention
(121)	8	Healthy volunteers	VFS-PM	No difference between supraglottic and control swallows
(151)	32	Supraglottic Laryngectomy & H&N Ca resections	VFS	Eliminated aspiration on 5ml boluses in 80% patients with H&N Ca
(152)	9	Post – supraglottic Laryngectomy	VFS	3/9 of the patients were able to eat orally at 2 weeks postoperatively & 7/9 were successful oral feeders by 3/12
(147)	1	H&N Ca	VFS	Prolonged airway closure but aspiration not eliminated

[6] PD= Parkinson's Disease; H&N Ca= head and neck cancer

2.4.3. Rehabilitation

Dysphagia rehabilitation includes interventions that are thought to result in permanent changes in the substrates underlying deglutition. As the nature of swallowing pathophysiology becomes better understood, there has been a sharp increase in the number of treatments targeting specific areas of breakdown. Management options for impaired UOS opening have developed considerably; albeit with varying evidence. Therapeutic programs designed to target impaired UOS opening include the Mendelsohn manoeuvre, Shaker "head-lifting" exercises and, most recently, jaw opening exercises.

(a) Mendelsohn Manoeuvre

The Mendelsohn manoeuvre was first described as a compensatory technique but, like the effortful swallow, is now regarded as a rehabilitative intervention (106). Perhaps the most challenging manoeuvre for patients to complete, the Mendelsohn manoeuvre involves purposeful prolongation of the anterio-superior displacement of the larynx at mid-swallow (139). Individuals with dysphagia are required to initiate the pharyngeal swallow and, at the peak of hyo-laryngeal excursion, maintain suprahyoid contraction before relaxing and completing swallow. This manoeuvre prolongs UOS opening and hence facilitates bolus flow in patients who present with impaired UOS opening and pyriform residue post swallow on VFS or FEES (Figure 2.11).

VFS studies have demonstrated that this manoeuvre maintains traction on the anterior sphincter wall to increase extent and duration of UOS opening in healthy volunteers and in people following brainstem stroke (139, 153). An initial case report of a forty-five year old patient with a medullary infarct demonstrated that the Mendelsohn improved swallow efficiency greater than two-fold over other techniques (153). When the Mendelsohn manoeuvre was originally investigated under VFS and PM in eight healthy subjects, there was a statistically significant increase in the extent (10.9-12.2 mm; $p<0.05$) and duration (0.58-0.75 secs; $p<0.05$) of UOS opening on a 10ml liquid bolus (139).

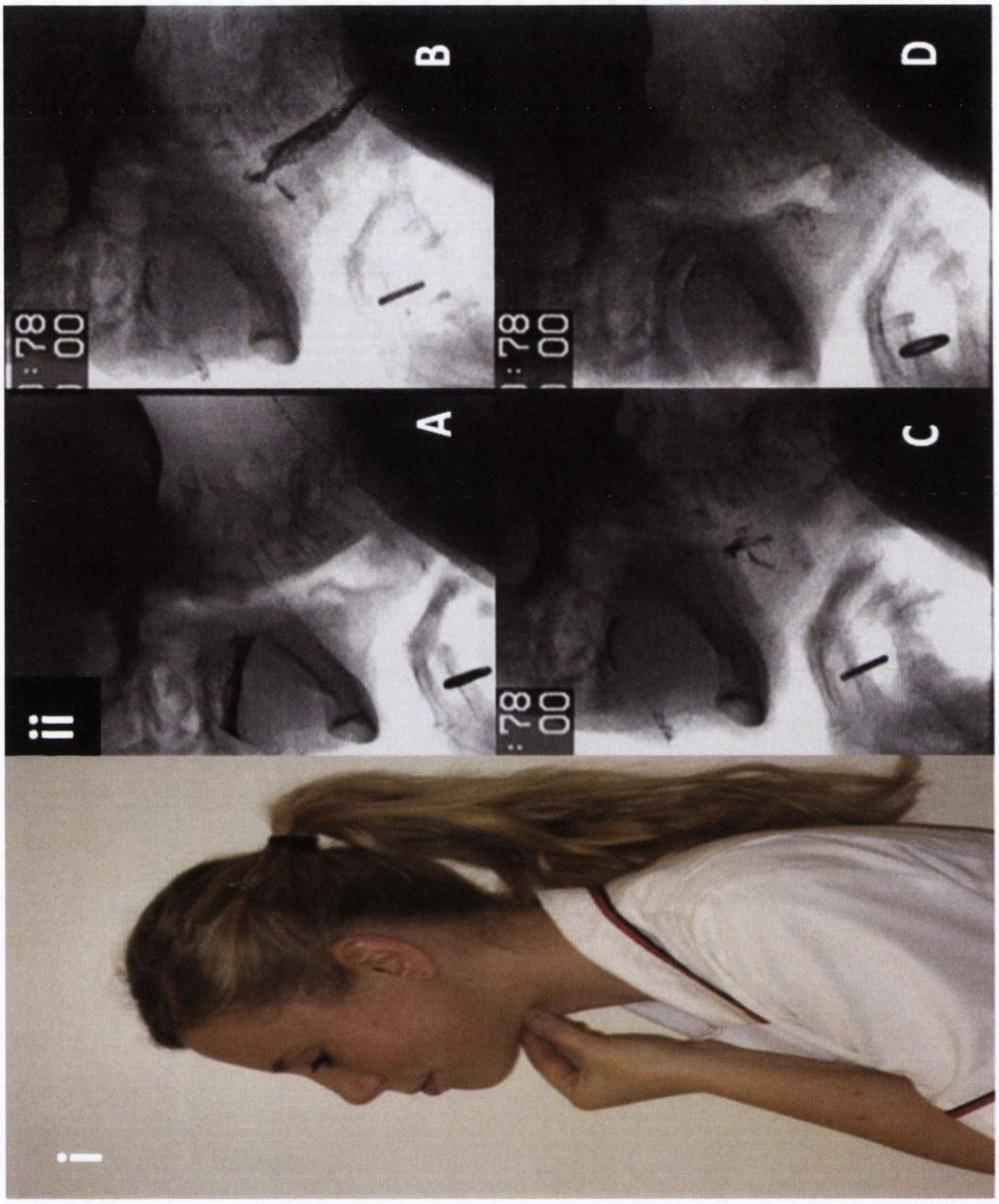

Figure 2.11 Demonstration of Mendelsohn Manoeuvre (i) and VFS Images of Mendelsohn Manoeuvre (ii)[7]

[7] In (i), Mendelsohn manoeuvre is demonstrated. In images A-D (ii), a seventy-three year old female with a history of stroke completes a swallow using the Mendelsohn manoeuvre during VFS. Note she places her fingers on her throat to obtain tactile biofeedback when completing the manoeuvre. There is prolonged suprahyoid contraction and hyo-laryngeal excursion which allows the bolus to transfer through the UOS with no pharyngeal residue or aspiration post swallow.

McCullough and Kim (2009) recently examined the effect of the Mendelsohn manoeuvre as a rehabilitation exercise on swallowing in eighteen individuals with dysphagia post stroke (154). Participants were randomised into two groups and received two weeks of intensive treatment (20 sessions) and two weeks of no treatment in a cross-over design study (AABB versus BBAA). Using VFS, authors established that participants showed modest clinical but statistically insignificant changes in extent of anterior (1.09-1.13cm) and superior (1.63-1.85cm) hyoid displacement and a negative change in extent of UOS opening (0.94-0.91cm)($p \leq .05$). Comparing across participants, there was a statistically significant improvement in extent of superior hyoid displacement. Participants showed modest clinical improvements in duration of hyoid maximum elevation, duration of hyoid maximum anterior excursion and duration of UOS opening.

In dysphagia practice, clinicians frequently have difficulty teaching the Mendelsohn manoeuvre to patients with dysphagia. Visual or tactile biofeedback has subsequently been used in rehabilitation to facilitate therapy (e.g., surface EMG). Change in suprahyoid muscle contraction has been established using the Mendelsohn technique in twenty healthy volunteers (155). The Mendelsohn manoeuvre was studied in a case series, quasi-experimental study of participants with a history of stroke using surface EMG biofeedback on suprahyoid musculature within sessions (156). Before treatment onset, 80% (20/25) of patients depended on non-oral feeding. Following treatment, 55% (11/20) had progressed to total oral feeding (156). A methodological flaw was the fact the minimum duration of time since stroke was not stipulated in the study. Mean duration of dysphagia was 24.8 months with just 72% of subjects having dysphagia for over six months. With these time frames, spontaneous recovery may have explained improvements in swallowing in some subjects post treatment.

Given the frequency with which the Mendelsohn manoeuvre is used in clinical practice, further objective evidence is required for this management strategy. Given the subjectivity associated with VFS analysis, this evidence-base may need to be sourced from physiological measures of swallowing. For any new clinical assessment to be useful, it needs to be a sensitive

outcome measure as well as a diagnostic tool. The Mendelsohn manoeuvre would, therefore, seem to be an important technique to explore in the development of any dysphagia evaluation technique.

(b) Shaker "Head Lifting" Exercises

The Shaker "head lifting" exercises are isokinetic and isometric manoeuvres designed to strengthen musculature involved in UOS opening during swallowing (Figure 2.12). The exercises target suprahyoid (i.e., mylohyoid, geniohyoid, and digastric involved in UOS opening) and infrahyoid muscles (i.e., thyrohyoid) (see Figure 2.4), which stretch open the relaxed UOS during swallowing. Initially, Shaker, Kern, Bardan, Taylor, Stewart, Hoffman et al (1997) studied thirty-one asymptomatic elderly (62-91 years) individuals using VFS, surface EMG and PM (157). Participants were studied before and after six weeks of either isometric-isokinetic head-lift exercise performed three times a day (n=19) or sham (n=12) exercises. All but one participant in the sham exercise group completed the six-week regime, however three volunteers reported mild neck pain within the first week which spontaneously resolved. Within the treatment group, there was a significant increase in anterior excursion of the larynx (15±1 to 19±1mm; $p<0.05$), UOS antero-posterior opening diameter (8.7±0.03 to 9.8±0.03mm; $p<0.05$), and a significant decrease in hypo-pharyngeal intra-bolus pressure post treatment (16±1 to 11±1mmHg; $p<0.05$). However, there were limitations to this study, including lack of supervision while the exercises were being completed over the six week period to ensure the exercises were being completed appropriately. Also, significant findings in this study were taken from small subgroups within the treatment group and did not reflect total treatment group effects.

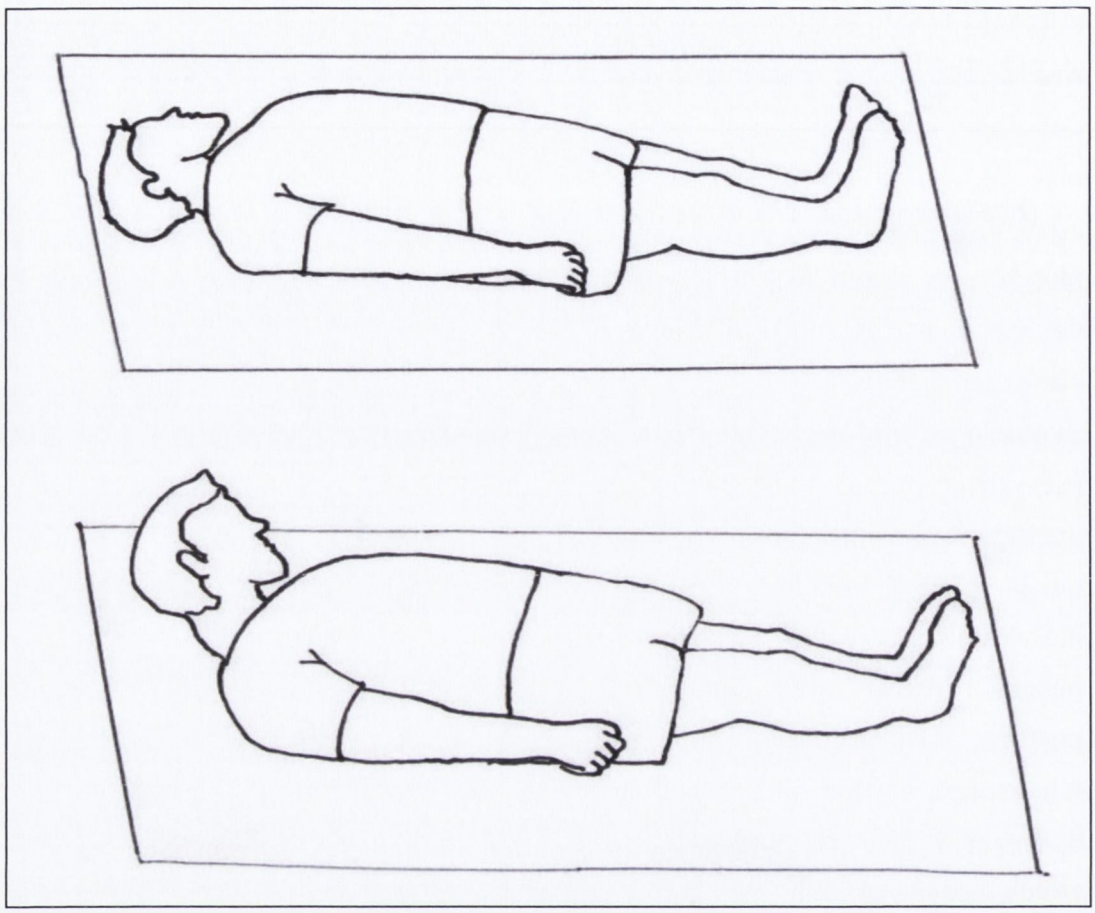

Figure 2.12 Shaker "head-lifting" Exercises[8]

Shaker, Easterling, Kern, Nitschke, Massey, Daniels et al (2002) subsequently evaluated the effect of the Shaker exercises on both swallowing and functional outcomes of swallowing in a group of twenty-seven patients with pharyngeal dysphagia of various aetiologies characterised by impaired UOS opening. Seven of 27 patients, assigned randomly, participated in a sham exercise before entering the exercise program and eleven were randomized to the Shaker exercises group. Again, neck pain was reported by study participants, which reportedly resolved spontaneously. While there was no change in swallowing after the sham

[8] Shaker exercises include isometric exercise where patients lie supine and raise the head "high enough to see toes" & sustain for one minute. This is repeated three times. Isokinetic exercises involve thirty repetitions of briefly raising & lowering head.

exercise, six weeks of the Shaker exercise led to significant improvement in each participant's UOS opening, anterior laryngeal excursion ($p< 0.01$), as well as resolution of post-deglutitive aspiration and they were able to resume oral feeding. Similar results were found when the seven patients in the sham group were crossed over to the real exercise group. Significant improvements were observed in antero-posterior UOS opening (5.1±0.5mm -7.2±0.5mm; $p <0.01$), anterior laryngeal excursion (11.8±2.0mm – 16.2±2.1mm; $p< 0.05$) and functional outcome assessment of swallowing as measured by the Functional Outcome Assessment Measure of Swallowing (FOAMS) ($p<0.01$) in the eleven participants randomised to the treatment group (158). However, significant methodological flaws were apparent in this study. Several individuals who remained in the acute phase post stroke (i.e., under three months post stroke) were recruited into the study. Improvement in swallow function may have been due to spontaneous recovery as opposed to any effect of the treatment.

In a recent randomised trial across seven settings, swallowing function was examined in nineteen individuals with dysphagia of at least three months duration before and after six weeks of Shaker exercises (n=8) or sham treatment (n=11) using VFS. However, only fourteen had VFS studies both before and after the six week period resulting in a dropout rate of 26% (5/19). Additionally, three of these fourteen participants were excluded as important landmarks were not visible on VFS. As a result, data from 11 patients (5=Shaker exercises; 6=traditional therapy) was analysed. Authors found less aspiration in the Shaker group post treatment (p=0.028) and an increase in UOS opening on 3ml paste consistency bolus only (p=0.015) (159). In contrast, there was no difference in post swallow residue between groups after treatment. Of note, the mean age varied across treatment and sham groups in this study. The effect of the Shaker Exercise on thyrohyoid muscle shortening has also been identified (160). Much research has been conducted to determine the effects of these exercises on swallowing and functional parameters. Findings have been inconsistent to date. Perhaps the use of a newer diagnostic tool may serve to objectively identify the effects of this treatment.

(c) Jaw Opening Exercises

A recent intervention study has demonstrated that jaw opening exercises can strengthen the suprahyoid musculature and hence improve UOS opening during swallowing (161). Eight adult patients with chronic dysphagia of various aetiologies were included in the study. Subjects were instructed to open the jaw to its maximum and hold this position for ten seconds. This exercise was repeated five times twice daily over a four week period. VFS was carried out pre- and post-treatment to determine change in hyoid elevation, UOS opening, pharyngeal residue post swallow and pharyngeal passage time. There was a statistically significant increase in superior ($p<0.05$), but not anterior ($p=0.05$), hyoid excursion and in extent of UOS opening ($p<0.05$) in all subjects. Pharyngeal passage time also decreased significantly post exercise ($p<0.05$) (161). A statistically significant decrease in pharyngeal residue was not found.

The significant effect of this jaw opening exercise on superior but not anterior hyoid movement is of interest as previous research has found that anterior hyoid movement is more directly related to UOS opening (72). Authors also did not examine the effect of exercise on duration of UOS opening. Also of note in this study, the inclusion criterion for subjects was UOS opening of less than 10mm during swallowing on VFS. However, the volume or the consistency of the bolus being swallowed for this measurement was not made explicit. Considering the effect of these and other variables on UOS opening and in order to ensure replication of the study protocol, this lack of information was a limitation. Of note, all subjects in this study were on an oral diet pre-treatment and so did not present with severe swallowing difficulties.

Based on VFS and PM data to date, the evidence base for rehabilitation strategies to improve UOS opening during swallowing are rather inconsistent. The development of a robust evaluation may help to determine their clinical utility.

2.4.4. Pharmacological Intervention

Only one pharmacological intervention was retrieved in the literature which is purported to target UOS opening during swallowing in individuals with dysphagia. This intervention is botulinum toxin, which will be described in detail below.

(a) Botulinum Toxin

There are two main types of botulinum toxin; botulinum toxin A (BoNT-A) and botulinum toxin B (BoNT-B). BoNT-A is a neurotoxin that inhibits pre-synaptic acetylcholine release and hence chemically denervates the motor endplate. This results in a temporally limited relaxation of the musculature. Schneider, Thumfart, Pototschnig & Engel (1994) were the first to describe the use of BoNT-A for the treatment of CP dysphagia (162). Seven patients with impaired UOS opening were treated with 80–160 units BoNT-A (Dysport®), with a success rate of 71% (162). Between 1994 and 2012, over thirty original studies have examined the efficacy of CP BoNT-A injection in around one hundred and fifty adults with dysphagia of varying aetiologies (Table 2.6) (Appendix 10.2).

Success rates of BoNT-A injections into the CP have varied between 43% and 100%. This may be, in part, due to inexplicit and subjective candidacy criteria based on current diagnostic evaluations (e.g., VFS) within studies and indeed in clinical practice. Fluctuating success rates may also be linked to different protocols across studies. BoNT-A brand and dosage (2.5-50 units Botox®; 60-360 units Dysport®), injection site, technique used to administer BONT-A (rigid endoscopy, flexible endoscopy, trans-cervical with EMG and trans-cervical CT-guided) and outcome measurements differ considerably across studies (see protocol for a Cochrane systematic review in Appendix 10.2). Nonetheless, BoNT-A usually brings improvement in deglutition, but most patients require reinjection in 3–5 months. For this reason, BoNT-A is often seen as a trial before committing to irreversible myotomy surgery (163). Side-effects from BoNT-A injections include inadvertent injection outside the CP which may result in temporary paralysis of the laryngeal musculature, causing dysphonia (hoarseness)

and, rarely, aspiration (164). The potential to cause adverse events; inconsistent research findings (Table 2.6) and the lack of clear and objective candidacy criteria for BONT-A injections into the CP muscle further demonstrate the need to develop a new and accurate diagnostic tool that is sensitive and accurate as well as useful as an outcome measure.

Table 2.6 Studies Investigating Botulinum Toxin A (BoNT-A) into CP Muscle to Improve UOS Opening

Study	Clinical Group	N	Test	E or TC+/ EMG[9]	BoNT-A Dosage	Outcome
(165)	PD, PSP, MSAx2, stroke, MS & ataxia telangiectasia.	34 (24-82)	Clinical & EMG (needle & surface)	TC+ EMG	15 units Botox Allergan on one side	50% significant improvement two months post treatment
(166)	6 x stroke; 1 x meningioma & 1 x chondro-sarcoma	8	VFS	6 x TC + EMG; 2 x E	100 IU Botox x 7 & 750 IU Dysport X 1	Improved pyriform residue. Tendency toward improvement in functional dysphagia scale
(167)	SAH, tracheostomy & PEG tube	1	Laryngo-scopic exam, VFS & PM	E	180 units Dysport (concentration = 200 U/ml)	Improved in 3/7 & oral intake for 6 weeks
(168)	7 brain lesions and 3 cervical spinal cord injuries	10	VFS & OM	E	100 units	Decrease in aspiration (3 x 1 yr). Improved UOS relaxation & pharyngeal contraction 6/10 eating exclusively by mouth at 3/12
(169)	Chronic stroke (ponto-cerebellar haemorrhage & R parietal ischaemic lesion)	2	FEES, VFS, OM, EMG, Oesophago gastro-duodenosc opy	TC+ EMG	25 units Botox Allergan & 15 units into each side of CP	Normal oral intake with Botox & rehabilitation

[9] E= endoscopic; TC+/- EMG= trans-cutaneous +/- EMG guidance; MSA= multi-systems atrophy; MS= multiple sclerosis; OM= oesophageal manometry; PD=Parkinson's disease; PEG=percutaneous gastrostomy; PSP= progressive supranuclear palsy; SAH= subarachnoid haemorrhage; SCC= squamous cell carcinoma; CNS= central nervous system; PND= peripheral nervous disease; IBM= inclusion body myositis; PMN=peripheral motor neuropathy; CEA=carotid endarterectomy; OGD= Oesophagastro- duodenoscope.

Study	Clinical Group	N	Test	E or TC+/ EMG[10]	BONT-A Dosage	Outcome
(170)	Type 2 diabetes. Severe dysphagia ass. with autonomic +/- peripheral somatic neuropathy	12	Clinical, VFS & simultaneous needle (EMG) of the CP and pharyngeal inferior constrictor (IC) muscles	TC+ EMG	30 Units Dysport (2ml dilution, 0.9% saline)	Complete recovery in 10 & some improvement in 2 within 4 +/- 1.1 days (range 3-7).
(171)	6 stroke, 1 post radiation, 1 MVA-craniotomy; 1 x H&N Ca; 1 x chemical inhalation; 2 x multiple neuropathy; 1 x progressive neural degeneration	13 (46-87 yrs)	VFS & FEES	TC+ EMG	100 units BTX A diluted in 2 ml sterile water 3 sites: CP, inferior constrictor, upper oesophageal musculature	12/13 overall improvement in ability to take oral diet safely (as per P-A scale). 9/12 resumed a normal oral diet.
(172)	8=CNS abnormalities, 5=PND 8=idiopathic	21	clinical, OM, upper gastrointestinal endoscopy, VFS	EMG	4-10 U BoTox	Dysphagia improved in 9 of 21 (43%) patients
(173)	Inclusion body myositis	2 (59 & 74 yrs)	Clinical, VFS & OM	OGD under conscious sedation	100 units Botox Allergan dissolved in 5ml saline into 4 sites	Improvement within 3-8 hours. Duration of response 6.4-8 months
(174)	8 x idiopathic; 1 polymyositis; 1 x brainstem infarction	10	Clinical & VFS	E under GA	30 units BOTOX Allergan injected in 3 portions into the posterior and both lateral sides of CP	UOS opening & clinical symptom scores improved in all patients. Hypopharyngeal retention or laryngeal penetration reduced x 4/7.

[10] E= endoscopic; TC+/- EMG= trans-cutaneous +/- EMG guidance; MSA= multi-systems atrophy; MS= multiple sclerosis; OM= oesophageal manometry; PD=Parkinson's disease; PEG=percutaneous gastrostomy; PSP= progressive supranuclear palsy; SAH= subarachnoid haemorrhage; SCC= squamous cell carcinoma; CNS= central nervous system; PND= peripheral nerve disease; IBM= inclusion body myositis; PMN=peripheral motor neuropathy; CEA=carotid endarterectomy; OGD= Oesophagastro- duodenoscope.

Study	Clinical Group	N	Test	E or TC+/ EMG[11]	BONT-A Dosage	Outcome
(175)	Brainstem stroke, IBM, CVA, PMN	4 (45-82 yrs)	Endoscopy & VFS (24 hr Ph & EM for 1 pt)	E under GA	14-50 units BOTOX Allergan into two areas of postero-lateral CP	¾ successful Duration ranged from 2 weeks to 12 months
(176)	Peripheral neuropathy, laryngectomy (CPM spasm) (isolated), stroke	12	VFS, PM and patient ratings	10 x E; 2 x open direct	25–50 Units BOTOX	Reduced barium retention on VFS. Improved patient ratings of dysphagia severity
(177)	2 x stroke & tracheostomy, base of tongue SCC & radiation, HIV+ & bilateral CEA	5 (all tube fed)	VFS, PM, videostrobo scopy, & FEES	Laryng - oscope & GA	40-100 units. Approx 20 units per injection. 1 x posterior midline and 2 laterally	4/5 long term benefits. Duration of benefit 2-14 mths
(178)	CP dysphagia; case III: CVA patient	5	Could not establish same	CT guided inject-ion	(first) 5 U, (second: 10 U); II: 10 U; III: 15 U (in only 1 side); IV: 20 U	2/5 (2 aspirated & 1 vocal cord paralysis)
(179)	Laryngectomy	5	Not explicit in abstract	Not in abstra ct	Not explicit in abstract	4/5
(180)	2 x stroke; 1 x partial pharyng-ectomy; 1 x Zenker's diverticulum; 1 x CP hypertonicity	6 (50-69)	Clinical, Ba swallow, fiberoptic laryngo-scopy	TC & EMG (1 x GA)	2.5 units in 1 cc x two sites on each side	All successful at 2 week follow up. Decrease of pooling of secretions in the hypopharynx.
(181)	CP/laryngeal dystonia; patients dysphagic with required feeding gastrostomy for almost a year	1 (86 yrs)	Could not establish same	EMG guided under VFS	16 units. 8 units each side.	"Striking functional recovery"
(162)	Stroke, H&N Ca, reflux disease	7	Clinical exam, cineradio-graphy & OM	E under GA & EMG	80-120 units Dysport, 0.4-0.8ml	5- Complete relief/marked improvement. 2 continued to aspirate

[11] E= endoscopic; TC+/- EMG= trans-cutaneous +/- EMG guidance; MSA= multi-systems atrophy; MS= multiple sclerosis; OM= oesophageal manometry; PD=Parkinson's disease; PEG=percutaneous gastrostomy; PSP= progressive supranuclear palsy; SAH= subarachnoid haemorrhage; SCC= squamous cell carcinoma; CNS= central nervous system; PND= peripheral nervous disease; IBM= inclusion body myositis; PMN=peripheral motor neuropathy; CEA=carotid endarterectomy; OGD= Oesophagastro- duodenoscope.

2.4.5. Surgical Intervention

Surgical approaches employed to treat UOS dysfunction comprise CP myotomy; upper oesophageal dilatation and, more recently, the Swallow Expansion Device (SED). Typically, patients need to have demonstrated little or no benefit from conservative management described in Chapters 2.4.2 and 2.4.3 before being considered for these more invasive interventions (Figure 2.8). Additionally, individuals with pharyngeal phase involvement (i.e., poor pharyngeal propulsion or weak hyo-laryngeal excursion) are generally not considered to be ideal candidates for these surgical interventions.

(a) Cricopharyngeal Myotomy

Cricopharyngeal (CP) myotomy is the most frequently used surgical technique to treat UOS dysfunction and aspiration (172, 182). The first CP myotomy was performed by Kaplan in 1951, for the treatment of a patient with post-polio dysphagia. It has since been used to treat dysphagia secondary to central and peripheral neurological disease, in head and neck cancer, muscular diseases, laryngeal and pharyngeal paralysis and structural disease (e.g., Zenker's diverticulum)(172, 183).

The procedure entails cutting the fibres of the CP muscle (typically 3-6cm length incision) to permanently open the sphincter (182). The classic approach to the external CP myotomy technique is performed under local or general anaesthesia. However, investigators have recently been exploring a trans-oral approach for endoscopic CP myotomy (184). Unlike the high efficacy of CP myotomy in patients with Zenker's diverticulum, the response to myotomy in pharyngeal dysphagia due to its neuromyogenic causes is only around 60%, with an operative mortality of 1.5% and a complication rate of 6% (185). Complications which may occur during CP myotomy include injury to the recurrent laryngeal nerve, which most often manifests as hoarseness after extubation and most often is due to a stretch injury to the nerve. Other complications include pharyngotomy, salivary fistula formation or recurrence of symptoms due to incomplete transection of

muscle fibres (182). Complications are related to poor patient selection due to inaccurate diagnosis or errors in the surgical technique.

While the evidence-base for CP myotomy is limited, it has been found to be most successful in patients with preserved or near normal pharyngeal function (182). In fact, surgery has been contra-indicated in those with marked pharyngeal weakness and those with significant GORD (182). This again highlights the need for precise diagnosis of the nature of impaired UOS opening during swallowing.

(b) Upper Oesophageal Dilatation

Oesophageal dilatation is a technique which is indicated in the treatment of symptomatic obstruction of the oesophagus. Dilatation treatments can be performed with a push dilator (bougie), a wire-guided polyvinyl dilator, air-filled pneumatic dilatation and water-filled balloon dilatation with or without endoscopic guidance (186). Balloon dilatation is frequently used in achalasia as it is cost-effective and the least invasive and troublesome approach. A polyethylene balloon mounted on a thin flexible bougie is passed over a guide wire. Radio-opaque rings mark the centre and ends of the balloon to facilitate placement using radiological screening. The dilators are available in three different balloon diameters ranging from 6 to 40 mm, and a graded approach starting with the smallest dilator is recommended (185). Balloon dilators are frequently used and can be passed through the scope or be wire guided. Dilatation is contraindicated in individuals with a history of oesophageal perforation, those who have undergone recent gastrointestinal surgery and those with pharyngeal or cervical deformity. It is also contraindicated in patients on anticoagulant medication (186).

(c) Swallow Expansion Device

Recently, researchers have proposed that the UOS can be manually controlled using a biomedical device (187). Anterior displacement of the larynx will cause anterior traction of the cricoid cartilage, thus expanding the anterior-posterior diameter of the UOS. To do this, the authors initially placed a suture around the cricoid cartilages of patients and found on VFS that anterior traction on the suture opened up the UOS.

Researchers subsequently developed a Swallow Expansion Device (SED) prototype for cadaver testing. A device comprised an implant secured to the cricoid cartilages of ten fresh cadavers and a corresponding hand-held magnet device was used that could be held over the implant across the skin. Five thousand pulls on ten cadavers ensured that the device did not damage the cricoid cartilage or surrounding area. Additionally, UOS opening using the device was ascertained using an Aero-sier airway sizing device (187).

Following on from these feasibility studies, six patients with oro-pharyngeal dysphagia and feeding tubes secondary to either stroke or head and neck cancer had the cricoid traction suture placed. Each of these patients had not benefited from traditional swallowing therapy. Anterior traction on the suture significantly improved UOS opening by 0.36 cm (±0.19 cm; $p<0.01$). It also eliminated aspiration in three of four patients who had aspirated without traction and three patients were discharged home with the suture in place in order to eat (187).

A final prototype of the SED was designed with an internal and external component. The internal component was a titanium-coated ferrous implant that secures to the cricoid cartilage via a small skin incision. An external magnetic device that affixes to the implant across intact skin was developed. This device houses a magnet which is used during swallowing. The device is held on the anterior cervical skin and is pulled forward during swallowing to manually open the UOS. While this research involves small sample sizes and is at a preliminary stage, it holds great promise for the future management of patients with impaired UOS opening during swallowing.

2.4.6. Conclusions

Each of the interventions described have been logically designed to manage impaired UOS opening and are being employed in clinical practice. However, their evidence base is, in most cases, limited to preliminary cohort studies and few level 1 (or randomised control trial) evidence. Consequently, there is much clinical uncertainty regarding candidacy for the

interventions, the optimal protocol to follow and the efficacy of these interventions. Unfortunately, some patients with dysphagia may be undergoing intensive rehabilitation which is unbeneficial or invasive surgery with potential adverse events while others may be deprived of beneficial care. Until the diagnostic evaluation of UOS dysfunction is developed further in an objective and accurate manner, uncertainty regarding indications for and benefits of these treatments will persist.

In the following section of this chapter, current methods to evaluate the UOS in clinical and research practice are reviewed.

CHAPTER 2.5. CURRENT EVALUATION OF UOS OPENING

2.5.1. Introduction

Validation studies have demonstrated that the bedside swallow evaluation (BSE) has poor diagnostic accuracy in identifying dysphagia and aspiration, let alone in recognising UOS dysfunction (188, 189). In fact, a recent systematic review demonstrated that the sensitivity and specificity of the BSE in detecting aspiration range from 27-85% (likelihood ratio (LR): 1.4-18.9) and 57-82% (LR:0.3-0.5) respectively (190). As a result, instrumental diagnostic techniques need to be conducted to examine specific aspects of swallowing such as UOS opening (51). Dysphagia evaluations generally fall into radiological, endoscopic, neurophysiological and gastrointestinal modalities. While VFS has historically deemed to be the "gold standard" dysphagia assessment, numerous technologies have since been developed or have been adapted from other clinical fields (e.g., gastrointestinal motility) to evaluate aspects of oro-pharyngeal dysphagia, including UOS opening. In clinical and research practice, these evaluations access different aspects of UOS function and they each contribute unique information to complement each other. This will ultimately help better our understanding of UOS function and disease.

Recently, instrumental developments are contributing to a better understanding of UOS dysfunction and more accurate and reliable diagnosis of UOS dysfunction. This is leading to the provision of more appropriate and effective dysphagia intervention. Despite these developments, the diagnostic accuracy of these evaluations in detecting disordered UOS opening during swallowing has not yet been fully determined. Many tests remain at the initial stages of validation (i.e., reliability and reproducibility of findings). Until validation studies are conducted against a robust reference standard, the delivery of optimal intervention continues to challenge most dysphagia clinicians. This chapter discusses in turn the various methods for examining UOS opening during swallowing. Each evaluation is critically reviewed in terms of (a) diagnostic accuracy; (b) outcome measurement and (c) limitations.

2.5.2. Radiological Evaluations

2.5.2.1. Videofluoroscopy

Videofluoroscopy (VFS) is the most available and frequently employed instrumental swallow assessment (191). This dynamic radiographic imaging assessment provides real time direct visualisation of bolus flow and structural movement during oral, pharyngeal and upper oesophageal phases of swallowing. Clinicians can determine the presence and underlying cause of aspiration and rate pharyngeal residue from VFS images (Figure 2.13). Clinicians can conduct frame by frame analyses of VFS examinations (ideally 25-30 frames per second) to measure extent and duration of UOS opening, anterior and superior hyoid displacement and pharyngeal strength during swallowing using kinematic analysis (i.e., measurement of oro-pharyngeal structural movement over time) (see Figure 2.13). In research laboratories, this is frequently carried out using software programs designed for measurement purposes (e.g., ImageJ or similar image processing programs) (192). Many clinical centres report that they do not have the facilities to complete frame by frame analysis from VFS recordings, which must complicate the acquisition of quantitative UOS opening measures. Where it is available, it is quite a time-consuming means of acquiring quantitative measures of swallowing.

(a) VFS as a Diagnostic Accuracy Tool for the UOS

Historically, VFS has been labelled the "gold standard" assessment of oro-pharyngeal swallowing. In the majority of validation studies, it serves as the reference standard for newer dysphagia diagnostic tools such as scintigraphy, FEES, HRM and MII in the detection of aspiration or pharyngeal residue (193-197). However, no studies have been found where VFS has been validated against other diagnostic tools (e.g., PM, EMG) to establish the diagnostic accuracy of its measurements of UOS function. Therefore, no data is available on the sensitivity and specificity of VFS in detecting UOS dysfunction. Despite this, indications suggest that it is low across all domains.

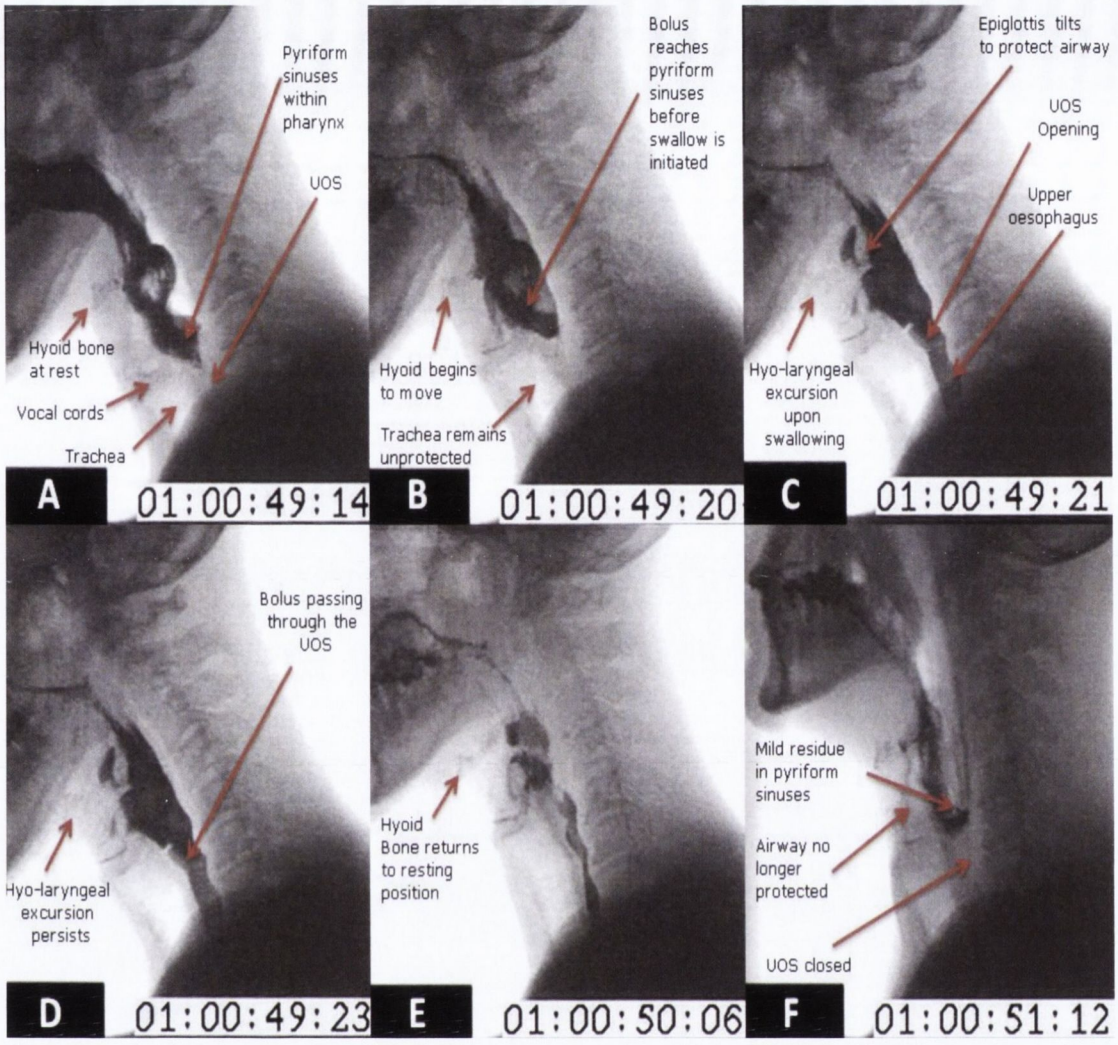

Figure 2.13 UOS Opening during Swallowing on Videofluoroscopy[12]

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[12] Six lateral VFS images over a two second period of 54 year old male with oro-pharyngeal dysphagia post stroke swallowing a liquid bolus. Note timer display in hours: minutes: seconds: frames (25 frames per second).
Image A Liquid barium bolus passes to the level of the pyriform sinuses before the pharyngeal swallow has been initiated. Note (i) UOS remains closed; (ii) hyoid bone and larynx are in resting position and (iii) airspace is evident between tongue base and posterior pharyngeal wall.
Image B Pharyngeal swallow is initiated. Hyoid bone is being pulled anteriorly and superiorly towards mandible due to suprahyoid and thyrohyoid muscle contraction. Tongue base begins to retract towards posterior pharyngeal wall to propel bolus through UOS. UOS has not yet opened.
Image C UOS opens (49.21) and bolus begins to pass into the oesophagus.
Image D Material continues to pass through UOS
Image E UOS closes (50.06). UOS opened for 10 frames (0.40 secs)
Image F Residue in valleculae and pyriform sinuses observed post swallow. Penetration of barium is visible to the level of the vocal cords.

(b) VFS as an Outcome Measure

Several studies have used VFS (alone or in combination with other evaluations) to investigate duration and extent of UOS opening during swallowing in healthy non-elderly adults across bolus volumes (44, 77, 84, 139, 198-202) (Figures 2.14 & 2.15). Interestingly, only one VFS study was found which measured UOS opening duration during dry swallowing, and it used combined manofluoroscopy (44) (Figure 2.15). The omission of dry swallow measures from VFS studies is due to the difficulty measuring UOS opening during dry swallowing without barium contrast in the UOS region (203). A critical issue in clinical practice is that VFS UOS opening measures present with poor inter and intra-rater reliability (Table 2.7).

Table 2.7 Reliability of VFS Measures of Swallowing[13]

Study	Raters	VFS Studies	UOS Parameter being measured	Inter-Rater Reliability Rating	Sensitivity Specificity
(204)	9 centres	n=51 Various causes	UOS opening time UOS closing time UOS opening UOS closing	0.22 Kappa score 0.03 Kappa score 0.42 Kappa score 0.04 Kappa score (acceptable level- 0.6)	Data not provided in study
(205)	3 SLTs	n=20 Stroke	CP function	75-92% agreement across 6 consistencies. Just 2 of 6 ratings at 90% or above (researchers unable to compute Kappa)	Data not provided in study
(206)	9 SLTs	n=3 2 MND, 1 normal	CP function	Mean Z score of 1.19 on semi-solids and 1.32 on fluids (insignificant)	Data not provided in study
(207)	4 physic-ians & 5 SLTs	n=20 Majority stroke	UOS opening	Positive predictive ratio of under 20%	Data not provided in study
(208)	10 SLTs	n=3 TBI; lateral medullar y stroke & cortical stroke	Impaired CP relaxation	1)100% agreement of absence 2)80-100% agreement of presence 3)100% agreement of absence	Data not provided in study
(209)	6 radiolog ists	n=72 Various aetio-logies	Incomplete opening of CP. Delayed UOS opening	0.69 Kappa score 0.40 Kappa score	Data not provided in study

[13] MND=motor neurone disease; TBI= traumatic brain injury

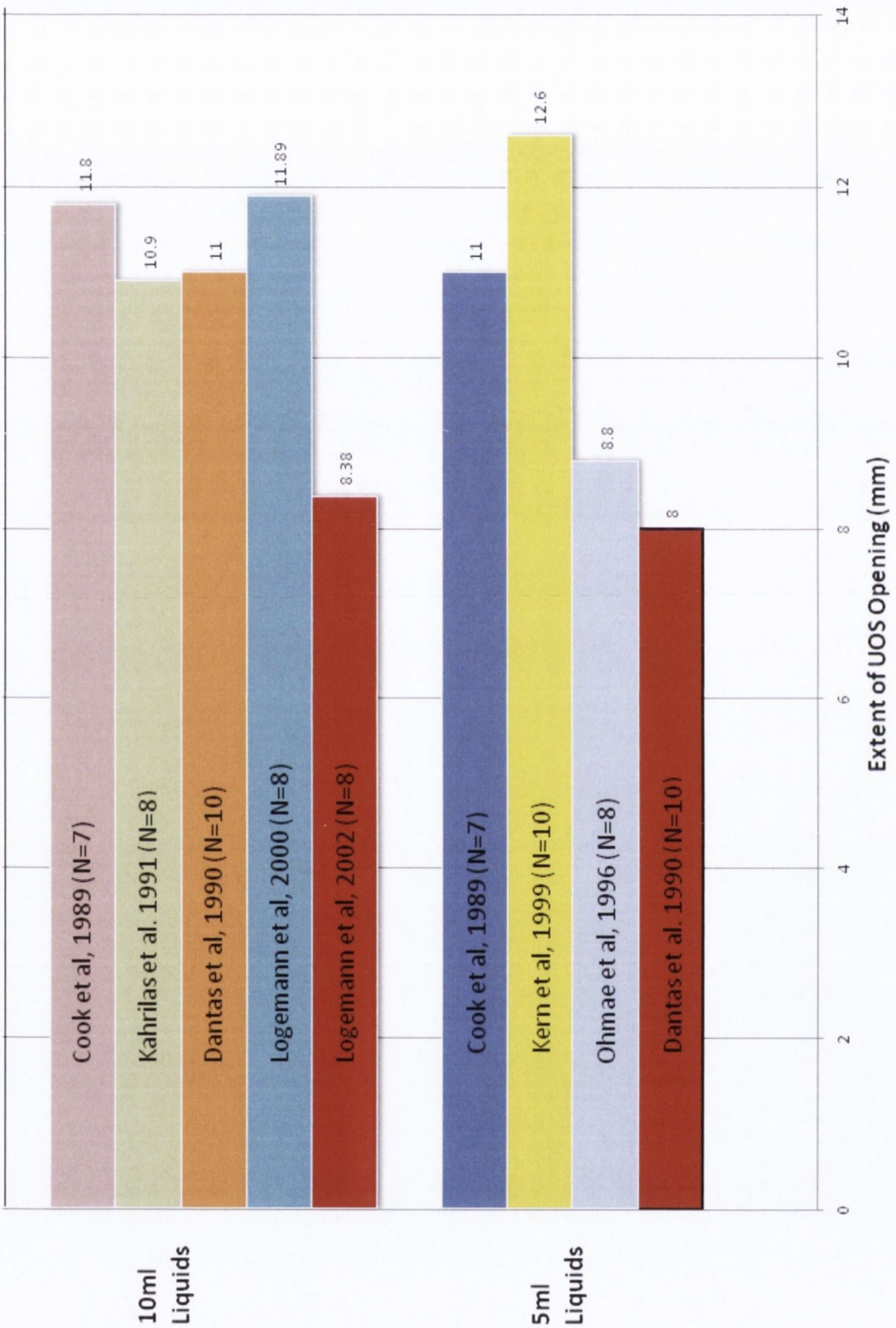

Figure 2.14 VFS Measures of Extent of UOS Opening in Healthy Adults

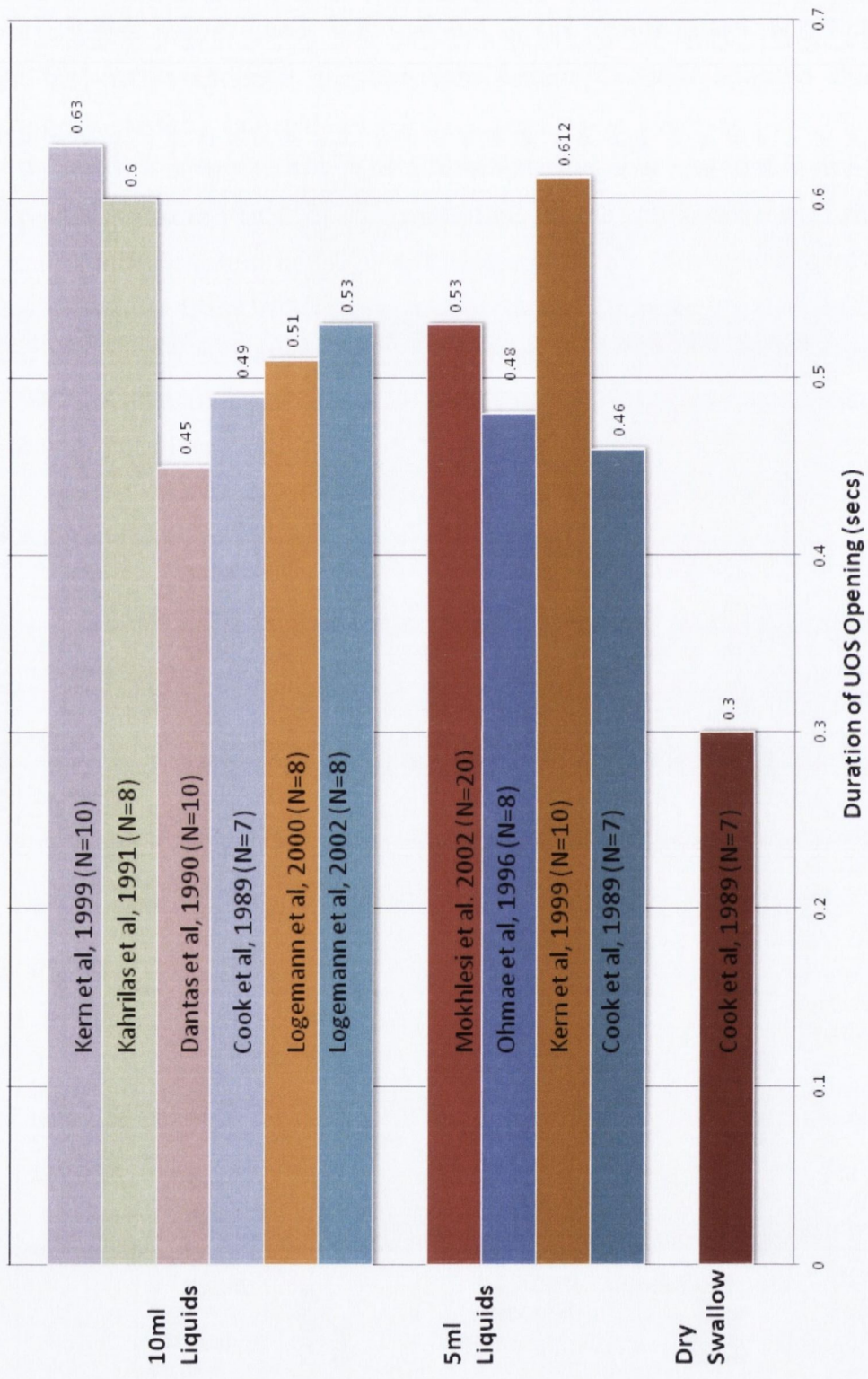

Figure 2.15 VFS Measures of UOS Opening Duration in Healthy Adults

Videofluoroscopic measures of extent and duration of UOS opening are considered by dysphagia researchers to be unreliable (204). Figure 2.14 demonstrates that extent of UOS opening measures can vary by over fifty percent across studies (i.e., 8mm to 12.6mm) (84, 198). While extent and duration of UOS opening measures range by just 4mm and 0.2 seconds respectively across studies (Figures 2.14 & 2.15), an increase or decrease of 4mm in extent of UOS opening and an increase or decrease in the duration of UOS opening by 0.2 seconds can drastically alter swallow safety and efficiency and the ability to eat or drink. Additionally, these varying ranges across studies obscure the identification of UOS dysfunction and any response to treatment in clinical practice. Clinicians internationally also currently experience great difficulty in deducing which phase of UOS opening is impaired based on VFS analysis. This limitation is fundamental as the nature of UOS impairment should guide dysphagia management (Figure 2.8). CP relaxation cannot be observed during VFS studies and hence other physiological evaluations need to be conducted before considering surgical or pharmacological interventions. Regarding hyo-laryngeal excursion, a meta-analysis of thirteen studies evaluating extent of anterior and superior hyoid displacement during swallowing was conducted which noted a wide variation in mean anterior hyoid displacement during swallowing from 7.6 to 18mm across studies (73). Mean superior hyoid displacement varied even more across studies with a range of 5.8 to 25mm (73). As normative values vary hugely, clinicians struggle to determine if hyo-laryngeal excursion is adequate when analysing VFS examinations. There is subsequently uncertainty regarding candidacy for and benefit from rehabilitation and, where rehabilitation is ineffective, candidacy for surgical intervention to ameliorate UOS opening.

Measurement of pharyngeal constriction, which is required to further distend UOS opening during swallowing, is also subjective during VFS analysis. It is generally gauged qualitatively by observing tongue base to posterior pharyngeal wall contact during the swallow and monitoring post swallow residue in the valleculae. In an effort to quantify pharyngeal constriction, the Pharyngeal Constriction Ratio (PCR) was devised as a "surrogate" measure of pharyngeal constriction during swallowing from VFS

studies (210). This involves measuring the unobliterated pharyngeal space remaining within the pharynx on VFS during a swallow at the point of maximum pharyngeal constriction and quantifying it using a software measurement program (PCR of >0.25 had pharyngeal clearing pressures of > 60 mmHg) (210). This measure is quite labour intensive however, and its use is currently restricted to research domains.

The issues regarding VFS measurement of different phases of UOS opening prevent clinicians from objectively or reliably deducing the underlying cause of impaired UOS opening. Therefore, the selection of an appropriate and effective intervention can regularly be limited to conjecture. This finding is disconcerting given that decisions regarding candidacy for invasive interventions (e.g., dilatation, BoNT-A injections) are regularly based on VFS examinations (166). This, once again, demonstrates the need for a new evaluation which can objectively capture extent and duration of UOS opening and can identify which phase of UOS opening is disordered.

(c) Limitations of VFS in UOS Examination

Data from VFS regarding extent and duration of UOS opening is certainly useful, however, it is widely recognised that, given the three-dimensional structure of the UOS lumen, including its radial asymmetry upon hyo-laryngeal excursion, kinematic measurement of UOS opening from a lateral two-dimensional VFS image is not an optimal means to evaluate UOS opening. It is also quite a time consuming mode of analysis in clinical practice which is frequently based on poor quality images. Measures vary depending on the frame rate available in different settings (25-29 frames per second). The need to add barium sulphate to the bolus being swallowed can impact on both the taste and the consistency of the bolus being swallowed which impacts on the generalisability of VFS findings (i.e., individuals may not have aspirated during VFS because the bolus being swallowed was a thicker consistency). As a result, it is unsurprising that multiple research studies have highlighted that VFS inter-rater reliability is at its lowest in UOS measurement (e.g., UOS opening times, incomplete opening, UOS function, impaired relaxation) (204, 207, 209, 211) (Table 2.7).

An accurate and time-efficient method of measuring extent and duration of UOS opening during swallowing is urgently required. The elimination of unnecessary radiation, labour intensive examinations with multiple team members, time consuming frame by frame analysis and transportation of patients to radiology would add to the clinical utility of a new diagnostic tool.

2.5.2.2. 320-Detector-Row Multislice Computed Tomography

320-detector-row multislice computed tomography (320-MSCT) has recently been employed to study the sequence of laryngeal events during swallowing including effects of volume and consistency on UOS opening during swallowing (212). Three-dimensional computed tomography (CT) images are created in 29 phases at an interval of 0.10 secs over a 2.90-secs duration. In a preliminary study of six healthy adults, UOS opening started 0.10-0.70secs after hyoid bone elevation, occurring during or at maximum hyoid displacement in all volunteers. UOS opening preceded the onset of laryngeal vestibule closure by 0.10s in four volunteers and was synchronized in two volunteers. Mean duration of UOS opening was 0.55± 0.10 secs. In another study of twenty-six healthy volunteers, UOS opening was significantly prolonged and started earlier with larger volumes (i.e., 20ml honey-thick barium).

(a) Multislice Computed Tomography as a Diagnostic Accuracy Tool for the UOS

No studies have been published to date which compare findings from multi-slice computed tomography to an established reference standard. The sensitivity and specificity of UOS opening measures obtained from this technique are, therefore, unknown at this point.

(b) Multislice Computed Tomography as an Outcome Measure

To date, no studies have presented data on either inter-rater or intra-rater reliability of swallowing measures including UOS opening. The slow frame rate must impact on the sensitivity of outcome measures.

(c) Limitations of Multislice Computed Tomography in UOS Examination

These research studies are very informative in terms of improving our understanding of deglutition, but the practicality of this evaluation for routine clinical use must be taken into account. Additionally, the potential effects of scanning posture (45 degree reclining position) and frame rate (0.10 s over a 2.90 second duration) should be considered.

2.5.2.3. Ultrasonography

Ultrasonography consists of high-frequency sound waves (1-40MHz) in order to obtain medical images. It is a tool used to evaluate muscle and soft tissue structures (e.g., abdomen, heart and foetus). Its many advantages include the fact that it is non-invasive, inexpensive and portable and it requires no barium contrast enhancement or ionizing radiation. Ultrasound was adapted to evaluate oro-pharyngeal swallowing in the 1970s, and initially focused on tongue movement. However, it has since been utilised to measure lateral pharyngeal wall motion and hyo-laryngeal elevation (10, 13). It has since been employed to obtain normative data on durational aspects of pharyngeal phases of deglutition in healthy adults (213).

(a) Ultrasonography as a Diagnostic Accuracy Tool for the UOS

A number of preliminary studies have been conducted to develop the diagnostic accuracy of ultrasonography in diagnosing numerous parameters of swallowing (214). The diagnostic accuracy of hyoid—larynx approximation (H-LA)(defined as distance obtained by subtracting the shortest distance between the hyoid bone and thyroid cartilage during swallowing from the initial resting distance) was investigated in ten stroke patients using clinical diagnosis and VFS as a reference standard (215). While a significant difference between ultrasonographic and videofluoroscopic measurement of change percentage of H-LA was not observed in this study (40.4%±7.1 and 42%±16.1 respectively; $p=0.45$), significant differences in specific measures of hyo-laryngeal excursion were observed between ultrasound and VFS (215). These included ultrasound and VFS measures of resting distance (3.48cm±0.53 and 2.00cm±0.41 respectively; $p<0.001$); shortest distance (2.04cm±0.35 and 1.13cm±0.24

respectively; $p<0.001$) and approximation distance (1.41cm±0.35 and 0.88cm±0.44 respectively; $p=0.008$). Decreased H-LA (<40% of resting distance) indicated dysphagia in this study. Based on videofluoroscopic analysis, ultrasonographic measurement of reduced L-HA had a sensitivity of 75% and specificity of 77.1% (PPV=65.2%; NPV 84.4%) in detecting dysphagia. Additionally, methodological issues acknowledged by the authors in this study included the fact that ultrasound examiners were not blinded. While measures of hyo-laryngeal excursion relate to one aspect of UOS opening, no study has focused directly on the diagnostic accuracy of ultrasound in measuring UOS opening.

(b) Ultrasonography as an Outcome Measure

Hyoid-larynx approximation (H-LA) can be calculated to gauge extent of hyo-laryngeal elevation during deglutition (215, 216). In an initial study of 42 adult healthy volunteers (mean age 57) and 18 patients with neurogenic dysphagia (mean age 63), mean distance between the hyoid bone and upper end of the thyroid cartilage was measured at rest (200mm±30mm and 185mm±45mm respectively; $p=0.105$) and during swallowing (85mm±11mm and 105±18mm respectively; $p<0.001$)(216). This technique therefore determined significant differences in hyo-laryngeal excursion between dysphagic and non-dysphagic groups (215, 216). Differences in hyo-laryngeal excursion as measured by ultrasonography were also found in a more recent study (215). Good inter-rater reliability (ICC 0.983) and intra-rater reliability (ICC>0.95) of ultrasonographic measurement of H-LA has also been established (215).

(c) Limitations of Ultrasonography in UOS Examination

Limitations reported in the literature include the limited scanning region, the inability to visualise bone (e.g., hyoid movement) and also aspiration cannot be identified during ultrasonography. It cannot derive information on UOS opening, CP relaxation or pharyngeal contraction in order to direct dysphagia management. Methodological issues include stabilisation of the transducer, head position of subjects and accurate identification of anatomical landmarks (217). It is therefore regarded as being a useful

complementary resource in dysphagia evaluation as opposed to a standalone diagnostic tool.

2.5.2.4. Scintigraphy

Scintigraphy is an imaging modality that records the passage of a radionuclide bolus through the upper digestive tract. It has been used predominantly in research as it can provide accurate measures of the amount of material being aspirated. It is also sensitive to aspiration secondary to regurgitation and allows refluxed material to be evaluated in patients with feeding tubes.

(a) Scintigraphy as a Diagnostic Accuracy Tool for the UOS

A number of preliminary studies have been completed to establish the diagnostic accuracy of scintigraphy against various reference standards including VFS and PM (193, 218, 219). Shaw, Williams, Cook, Wallace, Weltman et al (2004) prospectively validated findings from scintigraphy against VFS (193). Nine healthy male volunteers (mean age 23 yrs, range 18-25 yrs) and twenty-six patients with dysphagia (13 male, mean age 72, range 50-88 yrs) underwent scintigraphy and VFS within a one week period. Parameters tested included oral and pharyngeal transit times and oral and pharyngeal bolus clearance. Sensitivity and specificity of oral (6% & 97% respectively) and pharyngeal (24% & 96% respectively) transit times and oral (72% & 100% respectively) and pharyngeal (57% & 96% respectively) bolus clearance were inconsistent (no confidence intervals were presented). In another study, oral and pharyngeal residues from 16 individuals (mean age 75) with dysphagia of various causes during scintigraphy were compared to VFS measures obtained on the same day (218). Significant correlations were found between scintigraphy and VFS measures for oral ($r=0.66$) and pharyngeal ($r=0.60$-0.61) residue ($p<0.02$). Limitations to this study were that evaluations were not completed concurrently due to differences in the contrast medium needed across studies.

While pharyngeal bolus clearance measures could be indirectly related to UOS opening, no explicit measures of UOS opening were validated in this

study. No other studies were found which validated scintigraphy measures of UOS opening against a robust reference standard.

(b) Scintigraphy as an Outcome Measure

Scintigraphy can provide measures of percentage aspiration and percentage of oral and pharyngeal residue. In one study, bolus retention indexes were obtained for various phases of swallowing in a clinical group of patients with neurogenic dysphagia (n=19). These measures of bolus retention were found to be increased for oral (12.95%; p=0.0003), pharyngeal (15.05%; p=0.0003) and oesophageal (28.63%; p=0.002) phases of swallowing compared to healthy controls (n=17) (219). Scintigraphy also allows temporal measurement of the various phases of swallowing (219). In this same study outlined above, oral (1.45 secs; p=0.0005), pharyngeal (3.23 secs; p=0.044) and oesophageal (19.87 secs; p=0.005) transit times were significantly increased in a neurological groups compared to healthy controls (219).

(c) Limitations of Scintigraphy in UOS Examination

Scintigraphy cannot identify swallowing disorders or establish duration measures of swallowing (e.g., duration of UOS opening). It does not provide any information on anatomical structures; hence it cannot deduce the extent or duration of UOS opening. As it cannot visualise the hyoid bone or pharynx, it cannot establish the underlying cause of UOS dysfunction. This examination is also limited in terms of how many swallows can be analysed. Finally, specialised training is required in order to obtain accurate measurements.

2.5.3. Endoscopic Evaluation

2.5.3.1. Fiberoptic Endoscopic Evaluation of Swallowing (FEES)

Initially described in 1988 by Susan Langmore and colleagues, FEES is performed by passing a narrow fiberoptic endoscope trans-nasally and directly visualising pharyngeal, laryngeal and epiglottic movements during swallowing. It also assesses the presence of any pharyngeal retention of

liquids or solids after swallowing. Its advantages include lack of radiation and the ability to perform the examination at bedside or in the clinic. It allows visualisation of the pharyngeal mucosa, airway protection, vocal cord movement and secretory management. Fiberoptic Endoscopic Evaluation of Swallowing with Sensory Testing (FEEST) allows sensory testing to be completed by monitoring vocal cord response to air pulse stimulation.

(a) FEES as a Diagnostic Accuracy Tool for the UOS

Numerous validation studies have been conducted where FEES findings have been compared to VFS (194, 195, 220-223). However, these studies focused on parameters such as aspiration, pharyngeal residue, laryngeal elevation early spillover of material and reflexive cough. Measures of UOS opening obtained from FEES have not been validated against a robust reference standard.

(b) FEES as an Outcome Measure

During FEES examinations, reliable measures of aspiration and pharyngeal residue can be obtained using validated rating scales (e.g., Penetration Aspiration Scale) (224). Additionally, the extent of hyo-laryngeal movement during swallowing cannot be explicitly evaluated. FEES, therefore, has limited value in terms of explicit objective measures of UOS opening.

(c) Limitations of FEES in UOS Examination

The role of FEES in diagnosing UOS impairment is restricted due to the "white out period" observed during swallowing. This "white out period" prevents visualisation of UOS opening and the acquisition of any UOS opening measurements. Hence, any abnormality in UOS opening needs to be inferred from residue in the pyriform sinuses post swallow (225). Therefore, the underlying cause of impaired UOS opening cannot be ascertained from a FEES examination as CP relaxation and hyo-laryngeal excursion cannot be directly visualised. Nonetheless, pharyngeal constriction can be tested during FEES using the Pharyngeal Squeeze (PS) manoeuvre, a surrogate measure of constriction validated against the PCR on VFS (226). If PS is deemed to be absent or impaired, the individual may not benefit from surgical intervention.

2.5.4. Neurophysiological Tests

2.5.4.1. Needle Electromyography

While more frequently employed in research domains, needle EMG studies provide recordings of electrical activity within a single muscle or in muscle groups. Direct recordings can be obtained from specific muscles involved in swallowing. Specifically, needle EMG can evaluate CP relaxation during swallowing. The CP muscle can be tested (CP-EMG) to measure CP relaxation during swallowing (i.e., "rest" or "no rest") which is frequently absent or impaired in medullary disease (88). Trans-cutaneous CP-EMG is performed by inserting a concentric needle electrode in a posterior and medial direction from an entry point 1.5cm lateral to the palpable cricoid border (88). Relaxation of the CP muscle during swallowing should correspond with a brief period of silence (preceded and followed by small bursts) on EMG (Figure 2.16). The CP muscle then resumes its baseline state of tonic activity. Of note, needle EMG can also be used to determine the contribution of specific suprahyoid (i.e., mylohyoid, geniohyoid, stylohyoid, anterior belly of digastric) muscles to hyo-laryngeal excursion during swallowing (227).

(a) Needle EMG as a Diagnostic Accuracy Tool for the UOS

Perhaps surprisingly, no studies have been identified which have investigated the diagnostic accuracy of needle EMG to the CP muscle in detecting parameters of swallowing against a robust reference standard. One study compared needle EMG findings to piecemeal deglutition (division of a large volume bolus into two or more parts and swallowed successively) or "dysphagia limit" (maximum volume a person can swallow without piecemeal deglutition) in thirty healthy subjects and sixty patients with dysphagia (228). The specificity and sensitivity of this method were 100% and 95% respectively. However, piecemeal deglutition is not considered a robust reference standard such as VFS or FEES and hence this is seen as a major limitation to this study.

(b) Needle EMG as an Outcome Measure

Mean duration of rest period from tonic CP activity (CP-EMG pause) during swallowing in healthy adults has been reported to be 0.462 secs (229). This contrasts with CP pause duration of 0.359 secs in twenty-five patients with amyotrophic lateral sclerosis and dysphagia (229) and to a CP pause of 0.39 secs in thirty-one patients with dysphagia secondary to suprabulbar palsy and lacunar infarct (230). Unlike duration of UOS opening measures on VFS studies, duration of CP relaxation has not been shown to increase with larger bolus volumes (227). This may reflect the influences of pharyngeal events such as hyo-laryngeal excursion on duration of UOS opening.

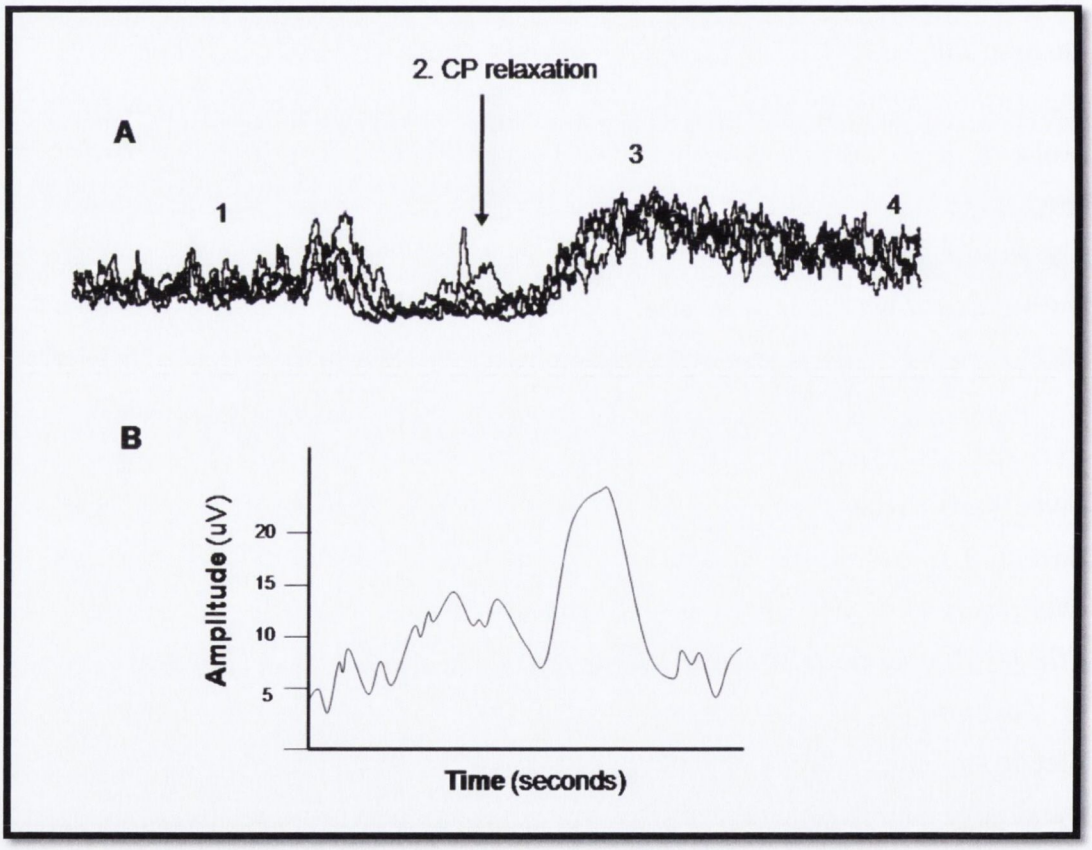

Figure 2.16 Electromyographic Evaluation of Swallowing[14]

[14] Line tracing A depicts needle EMG of CP muscle during swallowing. Line tracing B captures suprahyoid muscle contraction during swallowing as measured by surface EMG.

(c) Limitations of Needle EMG in UOS Examination

Electrophysiological evidence of isolated CP hyperactivity during the swallow has been shown to predict a good response to BoNT-A injections into the CP muscle (165). However, absent CP relaxation during swallowing can, in some cases, be compensated for at the pharyngeal phase of the swallow (e.g., increased or prolonged hyo-laryngeal excursion). This phenomenon has been observed in early stages of PD before any clinical features of dysphagia, and it is in keeping with recent research which found vagus nerve damage from early stages of the disease (231). Equally, individuals presenting with preserved CP relaxation may have impaired UOS opening due to weak hyo-laryngeal excursion or impaired pharyngeal contraction. And while hyo-laryngeal excursion can compensate for impaired CP relaxation, the reverse has not been reported. Needle EMG should therefore be combined with other investigations before determining optimal dysphagia management.

2.5.4.2. Surface Electromyography

Surface EMG (sEMG) is utilised to detect suprahyoid muscle group activity during swallowing related hyo-laryngeal excursion (128). Bipolar surface electrodes are placed over the submental region to measure peak amplitude (μV) and duration (ms) of muscle group contraction during hyo-laryngeal excursion (Figure 2.16). Reduced amplitude may indicate impaired hyo-laryngeal excursion.

(a) Surface EMG as a Diagnostic Accuracy Tool for the UOS

Two studies were found which investigated the validity and reliability of surface EMG measures of hyo-laryngeal excursion (232). However, neither of these studies compared these findings to a robust reference standard in order to determine the diagnostic accuracy of these surface EMG measures. No information is therefore available regarding the sensitivity and specificity of surface EMG measures of hyo-laryngeal excursion against VFS or another robust diagnostic tool.

(b) Surface EMG as an Outcome Measure

Research has established mean peak amplitude (57.3μV) and duration (924ms) of suprahyoid muscle contraction in thirty-five healthy adults on surface submental EMG (230). Reduced suprahyoid group activity may indicate that impaired hyo-laryngeal excursion may be contributing to poor UOS opening. In cases where suprahyoid contraction appears impaired, rehabilitation aimed at strengthening suprahyoid and infrahyoid musculature (e.g., Shaker head lifting exercises), may be more beneficial than BoNT-A injections or a CP myotomy. The effect of taste on amplitude and duration of suprahyoid muscle contraction has been established using surface submental EMG (233). In fact, surface EMG measurement of suprahyoid muscles correlates highly with ultrasound measurement of hyo-laryngeal excursion (214). Surface suprahyoid EMG signal has been found to correspond strongly with biomechanical events during swallowing on VFS (234).

(c) Limitations of Surface EMG in UOS Examination

While surface EMG is easy to use, electrode placement and the impact of tongue movement can confound readings (146). Variability within and across sessions has also been considered a drawback in terms of validity of the evaluation. Surface submental EMG also does not evaluate CP relaxation or pharyngeal propulsion. It is therefore regarded as a biofeedback tool as opposed to a diagnostic evaluation. Nonetheless, abnormal reduction and increased suprahyoid surface EMG have been associated with inefficacy of BoNT-A injections to treat dysphagia (165).

2.5.5. Gastrointestinal Evaluation

2.5.5.1. Pharyngeal Manometry

Solid-state PM provides quantitative information regarding the timing, extent and sequence of pressure events occurring during pharyngeal swallowing. Typically, a 2.1mm diameter catheter is passed trans-nasally and three sensors are positioned to measure tongue base to posterior pharyngeal wall pressures, inferior pharyngeal pressures and UOS pressure during swallowing (235). Line-tracings represent pressure change versus

time at these three designated loci. An "M-wave" is typically observed on the UOS pressure tracing during swallowing, representing hyo-laryngeal excursion, drop in sub-atmospheric pressure upon UOS opening and active CP contraction before the hyo-larynx returns to resting position.

(a) Pharyngeal Manometry as a Diagnostic Accuracy Tool for the UOS

Numerous studies have evaluated the diagnostic accuracy of traditional manometry in diagnosing oesophageal conditions (236, 237). However, no studies were found which established the diagnostic accuracy of solid-state PM measures of UOS opening against an established reference test such as VFS or FEES. This is a major limitation to PM as a UOS evaluation tool and further demonstrates the need to couple PM with other diagnostic tools during the evaluation process.

(b) Pharyngeal Manometry as an Outcome Measure

Resting UOS pressures in healthy volunteers range from 35-200mmHg (58, 59). Normative data has been obtained for mean UOS pressure drop (-11mmHg) and duration of UOS pressure change (0.73 secs) during swallowing in young healthy adults (235). Age, gender, acute stress and bolus volume and consistency have been found to influence pressure recordings (62, 85) and the effects of compensatory strategies (e.g., effortful swallow) on pressure changes during swallowing have been observed manometrically (235).

(c) Limitations of Pharyngeal Manometry in UOS Examination

While PM is growing in popularity as a dysphagia assessment tool, there are several restrictions to this evaluation technique. There is great variability in normal ranges of UOS pressure. This is presumably due to the influence of different manometry systems, catheter sizes and study protocols as well as the effects of age, gender and anxiety on basal UOS pressure (see Chapter 2.2.4). Additionally, orientation of pressure sensors on a solid-state probe is critical due to the marked radial asymmetry of the UOS (58). Fixed sensor location on the manometry probe can also be problematic in pharynges of varying length (85). The UOS makes a 2-2.5cm excursion during

swallowing, easily displacing a focal sensor from the narrow high pressure zone. Also, the manometric catheter itself can stimulate sphincter contraction when placed in the UOS (80).

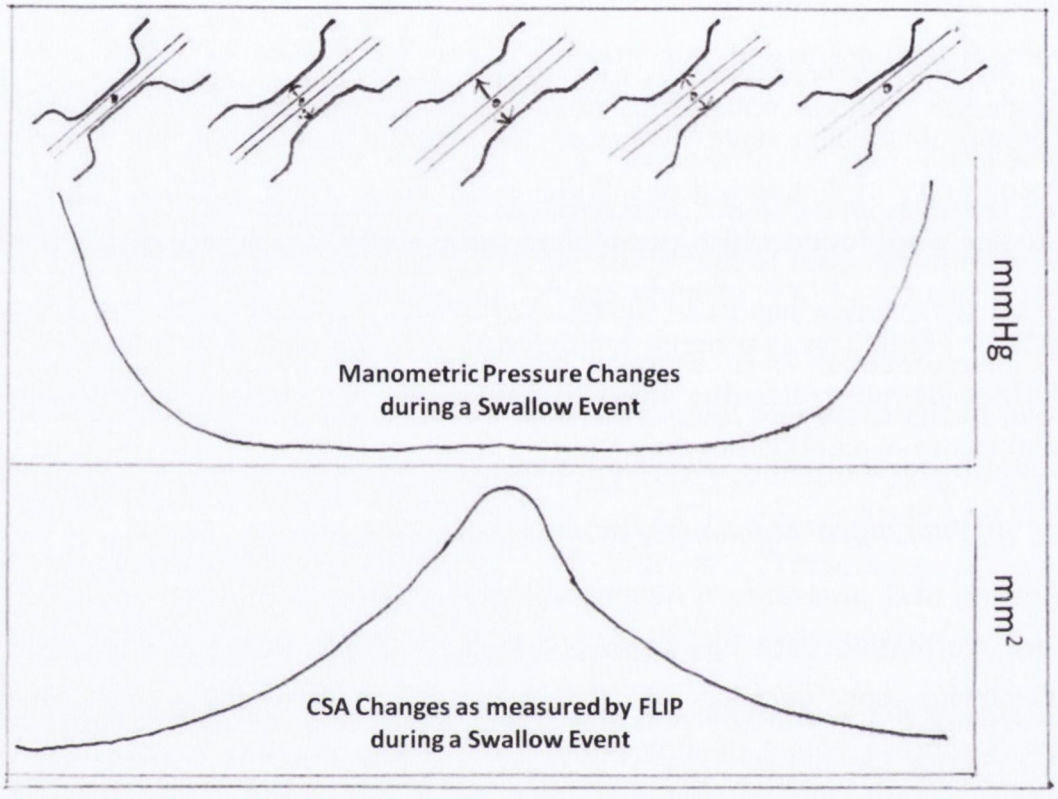

Figure 2.17 Changes in Manometric Pressure versus Change in UOS Cross-Sectional Area during Swallow[15]

Manometry evaluates "squeeze" on a probe sensor and hence determines the point and extent of UOS pressure drop preceding and during UOS opening (Figure 2.17). However, PM is unable to capture the degree of UOS opening once the UOS wall moves distally from the pressure sensor during swallowing. The UOS may only be opening to a fraction of its potential once it has broken contact from the pressure sensor, but because it is not in contact with the catheter; the extent of UOS opening cannot be captured.

[15] This image has been modified from McMahon, B. P., Jobe, B. A., Pandolfino, J. E., & Gregersen, H. (2009). Do we really understand the role of the oesophagogastric junction in disease?. *World journal of gastroenterology: WJG*, *15*(2), 144 238.
McMahon BP, Jobe BA, Pandolfino JE, Gregersen H. Do we really understand the role of the oesophagogastric junction in disease? World Journal of Gastroenterology: WJG. 2009;15(2):144.

In contrast, cross-sectional area measures can capture the extent of UOS opening during a swallow event (Figure 2.17). Limited conclusions regarding the extent and primary cause of impaired UOS opening and the most appropriate treatment plan can be made based on manometric findings alone. This may explain why PM is also not predictive of treatment success (183).

2.5.5.2. High Resolution Manometry

HRM is a promising new motility technique which has developed from traditional manometry. Its growing popularity is due to the presence of 36 sensors placed at 1cm intervals on solid state catheters, allowing for denser pressure profiles to be formed along the entire length of the pharynx and oesophagus, without concern for asymmetry or anatomic variation. These pressure profiles can be graphically represented into coloured spatio-temporal contour plots to visualize pressure–time relationships during the peristaltic progression (239). Spatiotemporal maps from HRM studies have simplified the interpretation of data and have led to the development of classification systems within disease groups (e.g., achalasia). Identification of subtypes within diseases has helped in the prediction of response to treatment.

(a) HRM as a Diagnostic Accuracy Tool for the UOS

While a small number of studies have been conducted to validate HRM in diagnosing oesophageal phase disorders, no studies have been completed to determine the diagnostic accuracy of HRM in isolation to detect UOS opening during swallowing against a robust reference standard (the diagnostic accuracy of combined HRM and MII will be reviewed in Chapter 2.5.5.4).

(b) HRM as an Outcome Measure

HRM has been employed to establish normative UOS pressures (e.g., maximum UOS resting pressure 70.2 +/- 30.0 mmHg) during swallowing in thirty-three healthy volunteers (240). It has also been employed to establish the effects of bolus volumes (saliva, 5ml, 10ml, 20ml) and compensatory strategies (head turn and chin tuck) on UOS timing and

pressure events in healthy controls (241, 242). HRM demonstrated that UOS pressure declination duration (0.85secs) increased, albeit insignificantly, with head turn (0.93secs) and chin tuck (0.89secs) postures.

(c) Limitations of HRM in UOS Examination

While HRM provides easy to interpret information regarding timing, extent and duration of UOS pressure changes during swallowing, it too is unable to offer explicit measurements regarding the degree of UOS opening during swallowing once sphincter contact is broken from the manometric pressure sensor. A drop in UOS pressure during swallowing may not mean the UOS has opened adequately for the bolus to transfer completely into the UOS. It also remains difficult, based on HRM evaluation alone, to differentiate between the effects of CP relaxation and hyo-laryngeal excursion on UOS opening. While combined HRM/VFS studies address some of these issues, questions regarding candidacy for surgical interventions can remain unanswered.

2.5.5.3. Multi-Channel Intraluminal Impedance

MII detects flow of liquids and gases throughout the pharynx, UOS and oesophagus by recording resistance to alternating currents measured between electrode pairs on an oesophageal catheter. MII has been used in dysphagia to detect impaired bolus flow throughout the pharynx, UOS and oesophagus (243). MII can also be combined with Ph studies to study gastro-oesophageal reflux disease (GORD) and with HRM to study bolus flow and pressure data without any need for radiation (Figure 2.18).

(a) MII as a Diagnostic Accuracy Tool for the UOS

No studies have been completed to determine the diagnostic accuracy of impedance in isolation to detect UOS opening during swallowing against a robust reference standard (the diagnostic accuracy of combined HRM and MII will be reviewed in 2.5.5.4.). Identification of bolus movement using MII has been validated against VFS (244). In a study of 15 healthy volunteers, impedance and VFS were in agreement with one of three bolus patterns (normal bolus transit, bolus stasis and retrograde escape) in 97%

(83/86) swallows. However, this study focused on OGJ instead of UOS bolus flow and no patient studies were included in this research.

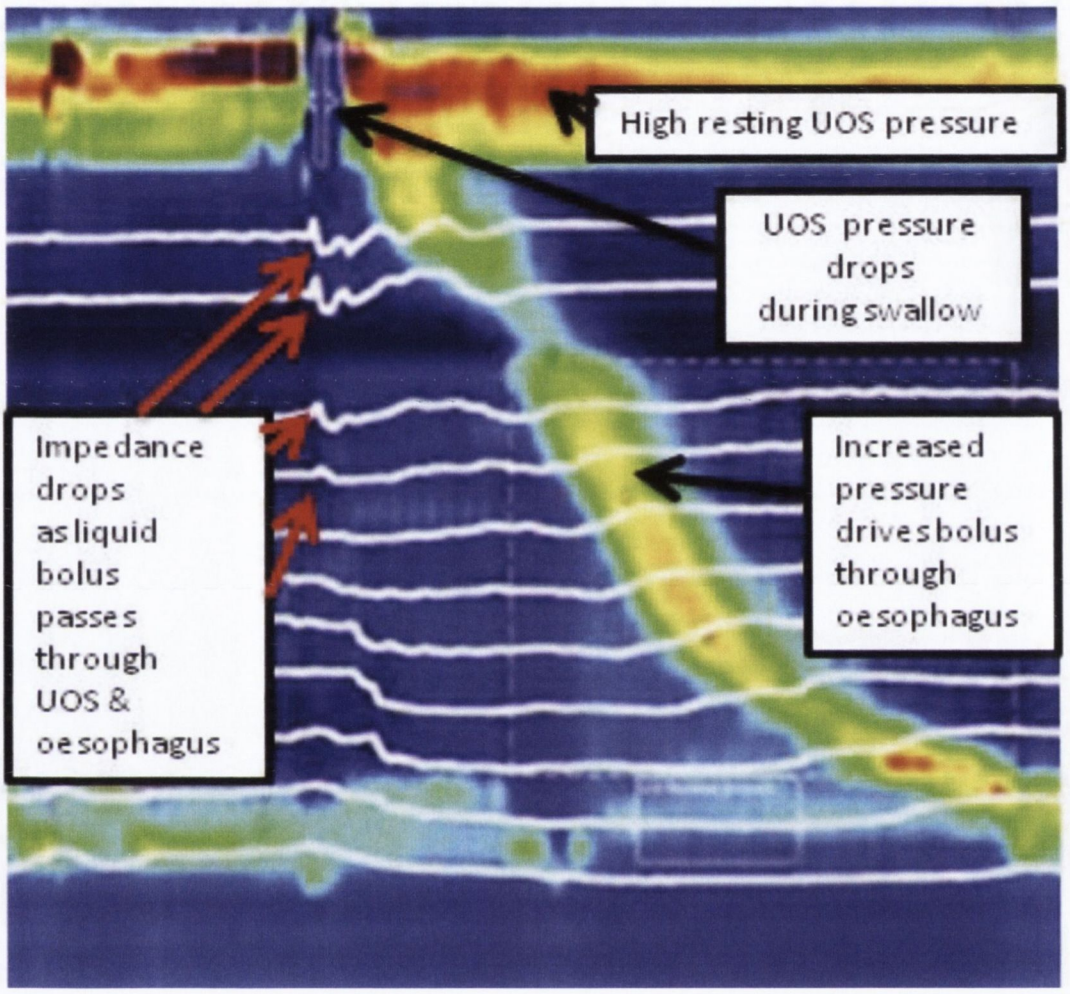

Figure 2.18 Combined High Resolution Manometry and Multi-Channel Intra-Luminal Impedance

(b) MII as an Outcome Measure

Changes in impedance can be interpreted as bolus transit; impedance rises during contact with a non-conductive bolus (e.g., air swallows, belches) and decreases with a conductive bolus (e.g., saline or refluxate). In studies to date, measures obtained from MII include bolus presence, bolus absence and nadir impedance during swallowing (243). Also, impedance can measure direction of bolus transit; hence measures of antegrade and

retrograde bolus flow can be obtained. No data on reliability of MII findings in the UOS region has been published (16).

(c) Limitations of MII in UOS Examination

MII is highly dependent on the ionic content of a bolus. Where study protocols include swallowing boluses of different ionic contents, results may not be comparable. MII cannot differentiate between CP relaxation and UOS opening. MII is not yet accessible to a large proportion of dysphagia clinicians. Perhaps as a result, there remains a paucity of information available on UOS normative data using MII, especially in the elderly. MII is unable to measure wall motion and hence cannot capture extent of UOS opening. Cause of impaired bolus clearance can also be unclear as the evaluation cannot differentiate between the various phases of UOS opening.

2.5.5.4. Automated Impedance Manometry Analysis

A study by Omari, et al. (2011) shows us that the combination of HRM and MII measurement provides valuable diagnostic parameters (245). Data achieved from HRM and MII measures is recorded on a computer. Subsequently, pharyngeal swallows can be captured into a CSV-file. Those CSV-files can be analyzed with *AIMplot* (Automated Impedance Manometry). AIMplot is a MATLAB-based analysis program, which derives four pharyngeal and UOS pressure-flow swallow variables (see Figure 2.19). AIMplot then combines those variables into a Swallow Risk Index (SRI). Out of the pressure colour iso-contour plot, three regions of interest (ROIs) are specified relative to the swallow onset, UOS relaxation and UOS high-pressure zone.

(a) AIM Analysis as a Diagnostic Accuracy Tool for the UOS

AIM analysis parameters based on combined HRM and MII have been validated against VFS (196, 197). Using AIM analysis, sensitivity and specificity of combined HRM and MII in detecting aspiration was 0.95 and 1 respectively. In a separate study, sensitivity and specificity of combined HRM and MII in detecting pharyngeal residue post swallow was 75% and 80% respectively.

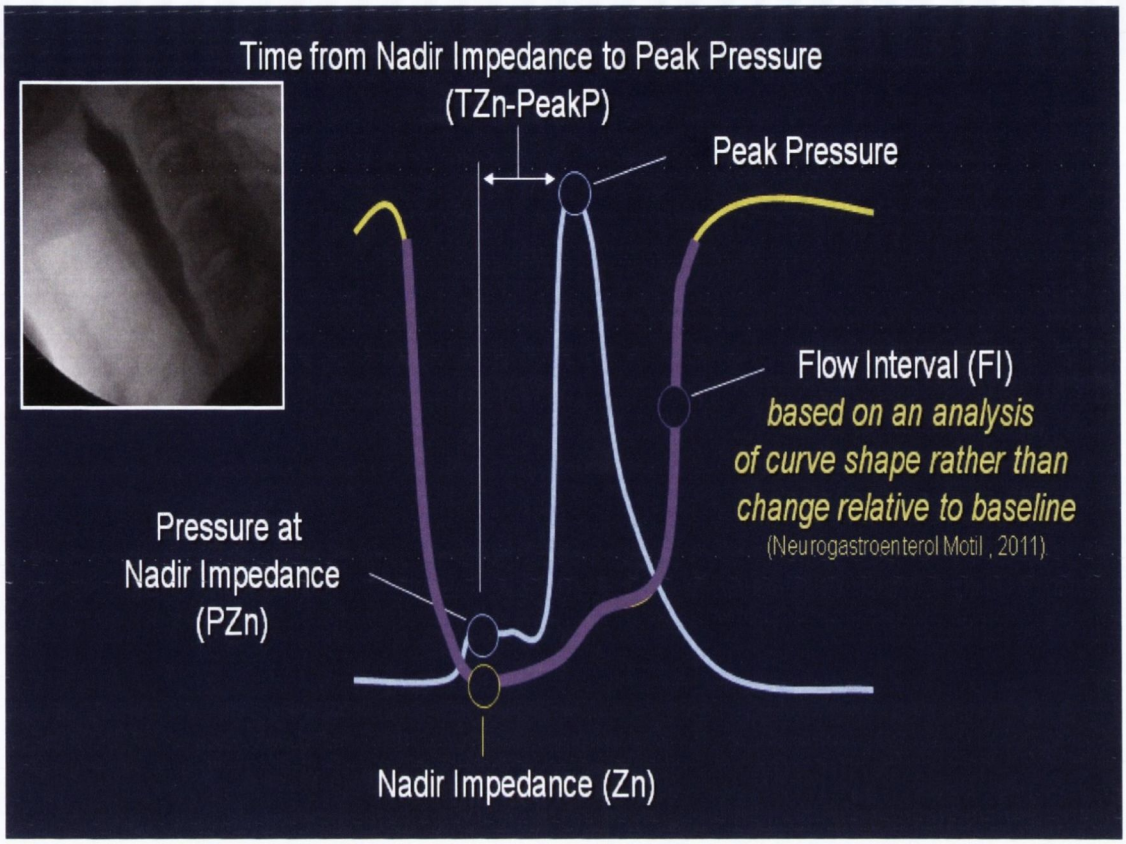

Figure 2.19 HRM and MII Measures included in AIM Analysis (blue line= manometric pressure; pink line= impedance)

More recently, AIM analysis parameters based on combined MII and HRM have also been validated against VFS to establish the sensitivity and specificity of AIM analysis in measuring UOS diameter during swallowing (246). In this study, manometry, impedance and VFS were used to measure liquid, semi-solid and solid bolus swallowing in forty individuals with dysphagia. Using the AIM analysis, combined HRM-MII measures were compared to videofluoroscopic measures of UOS opening. Of all the HRM and MII measures, UOS nadir impedance correlated most strongly with UOS opening from VFS, with narrower UOS diameters correlating with higher impedance ($r=-0.478$; $p<0.001$).

(b) AIM Analysis as an Outcome Measure

Parameters derived from combined HRM and MII for AIM analysis are depicted in Figure 2.19 (245). Four pharyngeal pressure-flow swallow variables are derived and combined into a swallow risk index (SRI) (Figure 2.19). The spatial limits of the pharyngeal stripping wave (from velo-

pharynx to proximal margin of the UOS high pressure zone) are identified by a region of interest (ROI) from the pressure iso-contour plot (Clouse Plot). The value and timing of pharyngeal peak pressure (PeakP) are measured and then the pressure at nadir impedance (PNadImp) and the time from PNadImp to PeakP (TNadImp-PeakP) are determined. The average PNadImp, PeakP and TNadImp-PeakP along the length of the pharyngeal segment are then calculated. The flow interval is an estimation of the duration of impedance drop within the distal pharynx within a second region of interest (ROI 2) from -0.25 to 2.5 secs of swallow onset (2, 3). The swallow risk index was developed based upon an iterative analysis evaluating the pattern of change in the four swallow variables in relation to the occurrence of aspiration. A higher SRI correlates with swallowing dysfunction and aspiration severity and a mean SRI of 15 or more for liquid swallows has been shown in neurological patients to be optimally predictive of aspiration risk (3, 4).

(c) Limitations of AIM Analysis in UOS Examination

AIM analysis is still at an early stage of research and hence cannot yet be deemed a gold standard test diagnostic tool.

2.5.5.5. AIM Analysis from HRM-MII as a Reference Standard Tool

HRM-MII and AIM analysis are relatively new investigations in themselves which, in the most part, are restricted to research domains. For this reason, they cannot yet be considered a gold standard evaluation for validation studies. Hence, any study using HRM-MII as a reference standard should be seen as comparative in nature as opposed to a true validation study. Nevertheless, combined HRM-MII is a viable reference standard for this research for the following reasons:

- AIM analysis has high intra-rater and inter-rater reproducibility (245).
- In contrast to VFS, AIM derives pharyngeal pressure-flow variables which are objective markers of swallowing. Through derivation of the

swallow risk index (SRI), it can predict ineffective swallows or swallows with aspiration risk (196, 197).

- Combined HRM-MII measures of UOS diameter are strongly associated with UOS opening measures derived from VFS (246).

Table 2.8 Benefits and Limitations to Instrumental UOS Evaluations

		Description	Benefits	Limitations
Radiology	Videofluoroscopy	Radiological exam providing real time and continuous viewing of the bolus during transit from the oral cavity and pharynx through the UOS and into the oesophagus.	Non-invasive. Available. Can detect anatomical abnormalities (e.g., stricture or pouch).	Subjective ratings-poor reliability. Difficult to measure asymmetrical UOS opening based on 2-d lateral images. Labour-intensive. Cannot be performed at bedside.
	Scintigraphy	Radionuclide test involving ingestion of bolus with radionuclide and movement recorded by gamma camera. Used to measure bolus transport and can detect retention and regurgitation post swallow.	Accurately measures the amount of material being aspirated. Sensitive to aspiration secondary to regurgitation and allows refluxed material to be evaluated in patients with feeding tubes.	Handling of radioactive material and radiation exposure. Lack of well-defined diagnostic criteria.
	UltraSonography	Provides visualisation of tongue movement and can measure hyoid-larynx approximation or hyoid-mandible distance to gauge extent of hyo-laryngeal elevation during deglutition. Normative data on durational aspects of pharyngeal phases of deglutition in healthy adults obtained (213).	Inexpensive and portable. No need for contrast enhancement or ionizing radiation. Has determined significant differences between dysphagic and non-dysphagic groups and it can establish effect of manoeuvres on aspects of swallowing (e.g., duration times) (215).	Limited by restricted views of many pharyngeal structures. It cannot derive information on UOS opening, CP relaxation or pharyngeal contraction to direct dysphagia management.

		Description	Benefits	Limitations
Endoscopy	**FEES**	Allows direct visualization of lingual, pharyngeal, and epiglottic movements during swallowing. Assesses the presence of any pharyngeal retention of liquids or solids after swallowing.	No radiation. Can complete at bedside. Can evaluate pharyngeal mucosa, airway protection, vocal cords and secretory management. Can carry out sensory testing.	No view of oral stage or upper oesophageal phase. White out period during swallowing prevents visualisation of UOS opening or hyo-laryngeal excursion.
Neurophysiology	**Needle EMG**	Needle inserted trans-cutaneously into individual muscles and direct recordings of electrical activity within a single muscle involved in swallowing provided (229). Specific muscle within the suprahyoid or infrahyoid region or the CP in the UOS can be tested to measure timing and degree of contraction or relaxation respectively during swallowing (88) (227).	Can quantify timing, extent and duration of individual muscle contraction (e.g., suprahyoid muscle) or relaxation (e.g., CP) during swallow. Has proven individual muscle benefit from rehabilitation (160). Can aid decision making regarding candidacy for BoNT-A injections into the CP muscle (165).	Invasive. Limited scope in terms of overall swallow ability- needs to be combined with other evaluations. Absent UOS relaxation during swallowing can, in some cases, be compensated for at the pharyngeal phase of the swallow. Limited availability.
	Surface EMG	Bipolar surface electrodes placed over targeted muscle group (e.g., submental region). Peak amplitude (μV) and duration (ms) of muscle group contraction during swallowing are recorded. Surface submental EMG can measure extent of suprahyoid muscle group activity to displace hyoid bone and larynx during swallowing (128).	Easy to use, non-invasive and inexpensive. Surface EMG measurement of suprahyoid muscles correlates highly with ultrasound measurement of hyo-laryngeal excursion and corresponds strongly with biomechanical events during swallowing on VFS (214) (234). Useful for biofeedback.	Electrode placement and tongue movement can confound submental readings (146). Variability within and across sessions. Used clinically and in research to evaluate swallowing but perhaps better placed as adjunct tool.

		Description	Benefits	Limitations
GI Motility	Solid-State Pharyngeal Manometry	2.1mm diameter catheter passed trans-nasally and 3 sensors measure tongue base to posterior pharyngeal wall pressures, inferior pharyngeal pressures and UOS pressure during swallowing (235). Provides quantitative information regarding timing, extent, duration and sequence of pressure events during swallowing (58, 59) (235). Line-tracings represent pressure change versus time at three loci.	Quantitative pressure data can be useful in detecting failure of UOS relaxation during swallowing. Can merge with VFS to observe CP relaxation before UOS opening observed.	Variability in normal ranges due to influence of age, gender, anxiety, volumes and consistencies, different manometry systems, catheter sizes and study protocols. Displacement and orientation of sensors during swallowing.
	High resolution Manometry	New technique developed from solid-state manometry. 36 sensors at 1cm intervals on solid state catheters allow denser pressure profiles are formed along entire length of pharynx and oesophagus, without concern for lumen asymmetry. Pressure profiles are graphically represented into coloured spatio-temporal contour plots.	Dense pressure profile and UOS not lost during swallow. Topographical plots easy to interpret. Seeing UOS in context of whole upper GI system. Can merge with VFS/MII.	Limited to changes in pressure-measuring squeeze behind bolus. Additional benefit of patient outcome undetermined as yet.
	Multi-channel intra-luminal impedance	Detects flow of liquids and gases throughout the pharynx and UOS by recording resistance to alternating currents measured between electrode pairs on an oesophageal catheter (247). Decreases in impedance are interpreted as conductive bolus transit (i.e., saline or reflux).	Bolus flow measures can be combined with manometric pressure data to detect pharyngeal retention and aspiration. Can be combined with Ph studies to study GORD and with HRM to combine pressure-flow data.	Noisy impedance signal in pharynx/UOS due to speed of pharyngeal swallowing, secretions, residue and sporadic mucosal contact (243, 248). Impedance changes with electrode width, diameter and spacing.

2.5.6. Conclusion

As outlined above, much of our knowledge regarding normal UOS function and UOS dysfunction has been obtained from videofluoroscopic, manometric and EMG studies. While these evaluations provide valuable information regarding UOS function, reliable or validated quantitative data is lacking in this area (Table 2.8). As a result, diagnostic testing is deemed a qualitative exercise and clinicians are advised to interpret current data cautiously (16). Until diagnostic evaluation is developed further, progress in our understanding and treatment of pharyngeal dysphagia will be hampered. If we refer to evaluation of the OGJ, it is only in the advent of HRM that specific subtypes of achalasia have been identified and refined treatments within each subtype have been developed. Researchers, therefore, agree that future work in the area of pharyngeal dysphagia and UOS dysfunction will likely centre on more accurate and physiologic diagnostic techniques. It is anticipated that this will ultimately improve intervention practices.

In Chapter 2.6, the aims, research questions and hypotheses for this research, which are based on this literature review, will be introduced.

CHAPTER 2.6. AIMS, RESEARCH QUESTIONS AND HYPOTHESES

2.6.1. Study Aims

Overall aim of this research was to adapt the EndoFLIP®, previously used to evaluate the OGJ, to evaluate UOS function. While the research questions have been briefly outlined in Chapter 1, they are expanded in this section and corresponding hypotheses are presented.

2.6.2. Research Questions and Hypotheses

The researcher addressed four key research questions in this thesis, each with supporting sub-questions. These research questions are based on the review of the literature reported earlier in Chapter 2. The questions address (1) EndoFLIP® data reproducibility and safety of EndoFLIP® testing; (2) the acquisition of normative data in a healthy adults, (3) the comparison of EndoFLIP® measures to an existing dysphagia evaluation and (4) the clinical utility of EndoFLIP® in UOS evaluation.

Specific research questions are outlined below. For research sub-questions where inferential statistics were employed (i.e., within research questions 2-4), alternative hypotheses are formulated. An alternative hypothesis is defined as a hypothesis which researchers attempt to demonstrate in an indirect way by use of a hypothesis test. If a null hypothesis is rejected, the alternative hypothesis is accepted. For ease of reference, see Table 2.9.

Research Question 1: Can EndoFLIP® provide accurate measures of the UOS and can it be safely positioned in the UOS in people with dysphagia and in healthy adults?

Three specific sub-questions to be addressed by the researcher were:

(A) What effect do balloon constriction and transducer position within the lumen of the balloon have on accuracy of EndoFLIP® diameter measurements?

Potential sources of error for EndoFLIP® measurement have been described in Chapter 2.1.6 and need to be addressed in this research before proceeding with further studies. The null hypothesis for this study was that there would not be adequate accuracy of EndoFLIP® diameter measures across varying transducer positions and balloon constrictions during accuracy testing.

(B) Can EndoFLIP® be safely inserted and positioned into the UOS in people with dysphagia?

The hypotheses for this study were that (i) EndoFLIP® could be safely inserted into the oesophagus without any serious adverse events (a serious adverse event is defined in this research as epistaxis, vasovagal event, airway compromise, respiratory distress or oesophageal perforation); (2) the distended balloon could be positioned in the UOS and distended under videofluoroscopic guidance until the hourglass shape of the UOS could be visualised on the EndoFLIP® screen and (iii) patients with dysphagia would be able to safely complete voluntary dry swallows and postural manoeuvres with the distended balloon in the UOS.

(C) Can EndoFLIP® be safely inserted and positioned into the UOS in healthy adults without videofluoroscopic guidance?

For this sub-question, the researcher hypothesised that (i) EndoFLIP® could be safely and accurately inserted and positioned in the UOS without VFS guidance and that (ii) subjects would be able to safely perform swallows and postural manoeuvres commonly employed in clinical practice with the

distended EndoFLIP® balloon in position in the UOS and (iii) preliminary temporal, diameter and IBP data relating to the UOS could be acquired.

Research Question 2: If yes, can EndoFLIP® provide normative data on UOS distensibility and UOS opening during swallowing in an adult healthy group?

Four specific research questions to be addressed in this study were:

(A) Is it possible to quantify UOS distensibility in an adult healthy group using EndoFLIP®?

The aim of this study was to use EndoFLIP® to provide new quantitative information on UOS opening characteristics during distension testing. Based on information in the literature review pertaining to the high tone of the UOS in healthy adults, the alternative hypotheses for this study were that UOS CSA would stop increasing significantly during distensibility testing and that there would be a statistically significant increase in IBP during balloon distension.

(B) Can EndoFLIP® quantify extent and duration of UOS opening across dry, 5ml and 10ml liquid boluses in an adult healthy group and can these EndoFLIP® measures be used to create colour contour plots of swallowing?

The alternative hypotheses were that (i) UOS diameter would increase significantly from baseline during dry and liquid swallowing; (ii) duration of UOS opening could be captured during swallow events; (iii) IBP would decrease significantly from baseline during dry and liquid swallowing and (iv) an increase in extent and duration of UOS opening and in drop in IBP would be observed with increasing bolus volumes. The researcher also hypothesised that (v) EndoFLIP® data could be used to create colour contour plots of swallowing measures.

(C) Are there gender differences in EndoFLIP® measures of UOS distensibility and UOS opening during swallowing in an adult healthy group?

The alternative hypotheses were that (i) significant differences in CSA and IBP would be observed across 1, 5, 10, 15 and 20ml balloon volumes during

ramp distensions and (ii) significant differences in UOS diameter, duration of UOS opening and minimum IBP would be observed across genders during swallowing across bolus volumes.

(D) Can EndoFLIP® evaluate the effectiveness of voluntary postures and manoeuvres frequently used in clinical practice to improve UOS opening during swallowing in an adult healthy group?

The alternative hypothesis for this study was that voluntary postures and manoeuvres commonly employed in dysphagia practice (chin tuck, head turn left and right, effortful swallow, Mendelsohn manoeuvre, supraglottic swallow) would alter the extent and duration of UOS opening during swallowing events and alter drop in IBP at rest and during dry, 5ml and 10ml liquid swallowing in an adult healthy group.

Research Question 3: How do EndoFLIP® measures of UOS opening during swallowing compare to an existing dysphagia evaluation such as High Resolution Manometry with Impedance?

In this study, the researcher hypothesised that EndoFLIP® temporal, diameter and pressure measures of UOS opening during swallowing would significantly correlate with data obtained from AIM analysis using combined HRM-MII in a group of healthy adults.

Research Question 4: What is the clinical utility of EndoFLIP® in dysphagia practice?

Two specific research questions to be addressed in this study were:

(A) What is the clinical utility of EndoFLIP® in a population of people with known UOS dysfunction?

Based on the literature review which described weak POS tone post total laryngectomy surgery, the alternative hypotheses for this study were that (i) there would be a statistically significant increase in POS CSA during distensibility testing whereas IBP would not increase significantly; (ii) during dry and liquid swallowing, POS diameter would increase significantly

from baseline and IBP would decrease significantly; (iii) significant differences in CSA and IBP would be observed during distensibility testing between the total laryngectomy group and healthy controls and (iv) significant differences in extent and duration of sphincter opening and in minimum IBP during swallowing would be observed between the total laryngectomy group and healthy controls.

(B) Are dysphagia-trained SLTs at an international level satisfied with current UOS evaluation and would they consider EndoFLIP® to be of benefit to dysphagia assessment and management?

Due to the exploratory nature of this study, a hypothesis was not formulated. The rationale for completing this survey was that, based on clinical experience, the majority of dysphagia clinicians are not satisfied with current UOS evaluation methods in clinical practice. This dissatisfaction is evident across respondents with varying levels of experience and from different countries and work settings. The nature of challenges in UOS evaluation reported by clinicians include lack of resources and equipment and limited access to current UOS evaluations (i.e., VFS, FEES, PM) internationally. Despite this, satisfaction levels with UOS evaluation have not been formally researched in the area of dysphagia. The researcher was also keen to determine, at this point, if data obtained from EndoFLIP® may be deemed useful by dysphagia clinicians to establish the effectiveness of dysphagia interventions. The researcher also sought to establish if the visual imaging of UOS and quantitative data derived from EndoFLIP® would be considered useful in dysphagia evaluation.

Table 2.9 Research Questions and Hypotheses

RESEARCH QUESTIONS	SUB-QUESTIONS	HYPOTHESES
1: Can EndoFLIP® provide accurate measures of the UOS and can it be safely positioned in the UOS in people with dysphagia and in healthy adults?	(A) What effect do balloon constriction and transducer position within the lumen of the balloon have on accuracy of EndoFLIP® diameter measurements?	There is adequate accuracy of EndoFLIP® data across varying transducer positions and balloon constrictions during testing.
	(B) Can EndoFLIP® be safely inserted and positioned into the UOS under videofluoroscopic guidance?	(i) EndoFLIP® can be safely inserted into the oesophagus without any serious adverse events; (ii) the distended balloon can be positioned in the UOS and distended under videofluoroscopic guidance until the hourglass shape of the UOS could be visualised on the EndoFLIP® screen (iii) people with dysphagia can safely complete dry swallows and postural manoeuvres with the distended balloon in the UOS.
	(C) Can EndoFLIP® be safely inserted and positioned into the UOS in healthy adults without videofluoroscopic guidance?	(i) EndoFLIP® can be safely and accurately inserted and positioned in the UOS without VFS guidance (ii) subjects can safely perform swallows and postural manoeuvres commonly employed in clinical practice with the distended EndoFLIP® balloon in position in the UOS (iii) preliminary temporal, diameter and IBP data can be acquired.
2: If yes, can EndoFLIP® provide normative data on UOS distensibility and UOS opening during swallowing?	**(A)** Is it possible to quantify UOS distensibility in an adult healthy group using EndoFLIP®?	(i) UOS CSA would stop increasing significantly during distensibility testing and that IBP would increase significantly during balloon distension.
	(B) Can EndoFLIP® quantify extent and duration of UOS opening across dry,	(i) UOS diameter will increase significantly from baseline during dry and liquid swallowing; (ii) duration of UOS opening can

	5ml and 10ml liquid boluses in an adult healthy group and can these EndoFLIP® measures be used to create colour contour plots of swallowing?	be captured during swallow events (iii) IBP will decrease significantly during dry and liquid swallowing; (iv) an increase in extent/duration of UOS opening and a drop in IBP will be observed with increasing volumes and (v) EndoFLIP® data can be used to create colour contour plots of swallowing measures
	(C) Are there gender differences in EndoFLIP® measures of UOS distensibility and UOS opening during swallowing in an adult healthy group?	(i) Statistically significant differences in CSA and IBP will be observed across 1, 5, 10, 15 and 20ml balloon volumes during ramp distensions (ii) Statistically significant differences in UOS diameter, duration of UOS opening and minimum IBP will be observed during swallowing across bolus volumes.
	(D) Can EndoFLIP® evaluate the effectiveness of voluntary postures and manoeuvres frequently used in clinical practice to improve UOS opening during swallowing in an adult healthy group?	Voluntary postures and manoeuvres (chin tuck, head turn left and right, effortful swallow, Mendelsohn manoeuvre, supraglottic swallow) will alter the extent and duration of UOS opening during swallowing events and alter drop in IBP at rest and during dry, 5ml and 10ml liquid swallowing in an adult healthy group.
3: How do EndoFLIP® measures of UOS opening during swallowing compare to an existing dysphagia evaluation such as High Resolution Manometry with Impedance?	N/A	There will be statistically significant correlations between EndoFLIP® temporal, diameter and pressure measures of UOS opening during swallowing and data obtained from AIM analysis using combined HRM-MII in a group of healthy adults.
4: What is the clinical utility of EndoFLIP® in dysphagia practice?	**(A)** What is the clinical utility of EndoFLIP® in a population of people with known UOS dysfunction?	(i) there will be a statistically significant increase in POS CSA during distensibility testing whereas IBP will not increase significantly;

		(ii) during dry and liquid swallowing, POS diameter will increase significantly from baseline, duration of POS opening can be measured and IBP would decrease significantly; (iii) significant differences in CSA and IBP will be observed during distensibility testing between total laryngectomy group and healthy controls and (iv) significant differences in extent and duration of sphincter opening and in minimum IBP during swallowing will be observed between total laryngectomy group and healthy controls.
	(B) Are dysphagia-trained SLTs at an international level satisfied with current UOS evaluation and would they consider EndoFLIP® to be of benefit to dysphagia assessment and management?	No hypotheses required due to survey design and descriptive analysis. Rationale for survey described in Chapter 2.6.2.

2.6.3. Conclusion

The aim of this research was to adapt the EndoFLIP®, previously used to evaluate the OGJ, to evaluate UOS function. This tool is user friendly, cost effective and portable, thus eliminating the need for radiation. The acquisition of new data on the UOS may complement data from existing evaluations and help to further develop our understanding of UOS function and dysfunction. Advancement in knowledge will lead to better delivery of care to individuals with dysphagia, leading to better clinical and healthcare outcomes. In the next chapter, methods to address these research questions will be described.

CHAPTER 3. METHODOLOGY

3.0. INTRODUCTION TO METHODOLOGY

Research into the adaptation of the EndoFLIP® probe for UOS evaluation has been justified in previous chapters. This methodology is based on the four major research questions outlined in Chapter 2.6.2. The methodological design for each research question will be described in sequential order. At the end of this chapter, the methodology is summarised (Chapter 3.6 & Table 3.6).

3.1. Ethical Approval

Ethical approval was sought by the researcher and obtained in a single submission in 2009 for all human studies (i.e., VFS studies, all healthy control studies and clinical laryngectomy studies) from St. James'/Adelaide and Meath including the National Children's Hospital Joint Research Ethics Committee (JREC) (see Appendix 4). It subsequently transpired that pilot studies and healthy control studies would take place in Leuven (i.e., research questions 2 and 3). Ethical approval was therefore also sought and obtained from the local ethics committee in Leuven (Research Ethics Committee, University Hospitals Leuven, Belgium) (see Appendix 4).

3.2. Research Question 1: Can EndoFLIP® provide accurate measures of the UOS and can it be safely positioned in the UOS in people with dysphagia and in healthy adults?

To address this first key research question, three sub-questions needed to be addressed. The questions and methodology associated with these three questions are described below.

3.2.1. The effect of transducer position within the lumen of the balloon and balloon constriction on accuracy of EndoFLIP® diameter measurements

In order to test accuracy of EndoFLIP® data, two bench-top experiments were designed which were based on potential sources of error already described in the Chapter 2.1.6. The null hypothesis for accuracy studies was

that there would not be adequate accuracy of EndoFLIP® data across varying transducer positions and balloon constrictions during testing. For the purposes of these studies, adequate accuracy was defined as a maximum percentage difference of 5% between diameter measures across conditions.

(i) Transducer Position Test

The first accuracy test was designed to examine (i) the effect of sudden change in wall diameter and (ii) deviation of electrodes from the central longitudinal axis on accuracy of EndoFLIP® measures.

3.2.1.1. Equipment

The EndoFLIP® system and the standard EF-325 EndoFLIP® probe were used for testing. A polymethylmethacrylate (Perspex®) diameter measuring block containing four cylindrical cavities with diameters of 7.60, 9.80, 11.90 and 15.80mm was used (Figure 3.1).

3.2.1.2. Procedure

A straight line was drawn onto a white piece of paper, which corresponded to a 0° angle. The measuring block was placed on top of the paper, and aligned such that the 0° line bisected the horizontal axis of the smallest cavity (7.60mm diameter). The block was fixed in position using a clamp.

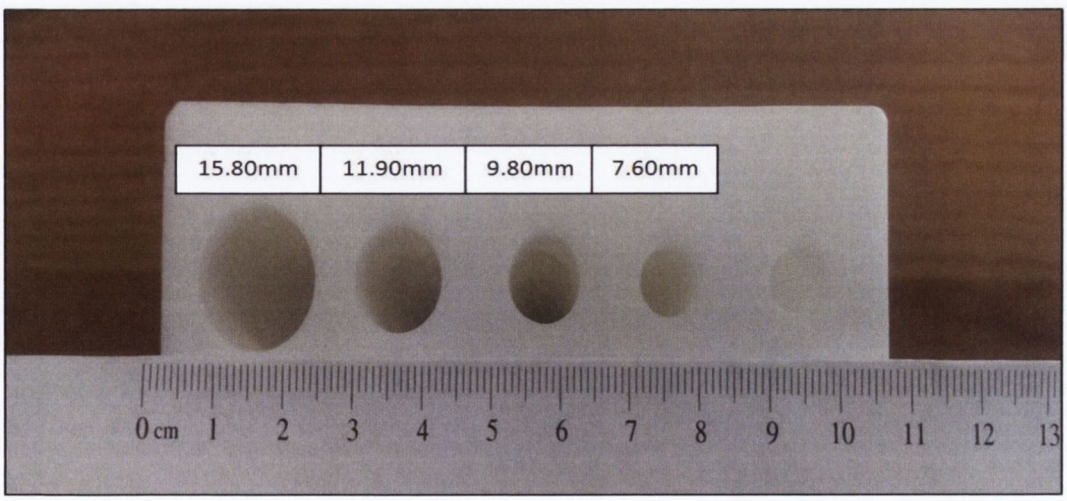

Figure 3.1 Measuring block with diameter of cylindrical cavities indicated

The EndoFLIP® balloon probe was inserted through the 7.60mm cavity until approximately 15mm of the balloon probe was visible on each side (Figure 3.2) and the balloon was aligned with the 0° line so that it was in the centre of the cavity. The balloon was inflated until the pressure was held constant at 15mmHg ± 2mmHg, as observed on the EndoFLIP® monitor.

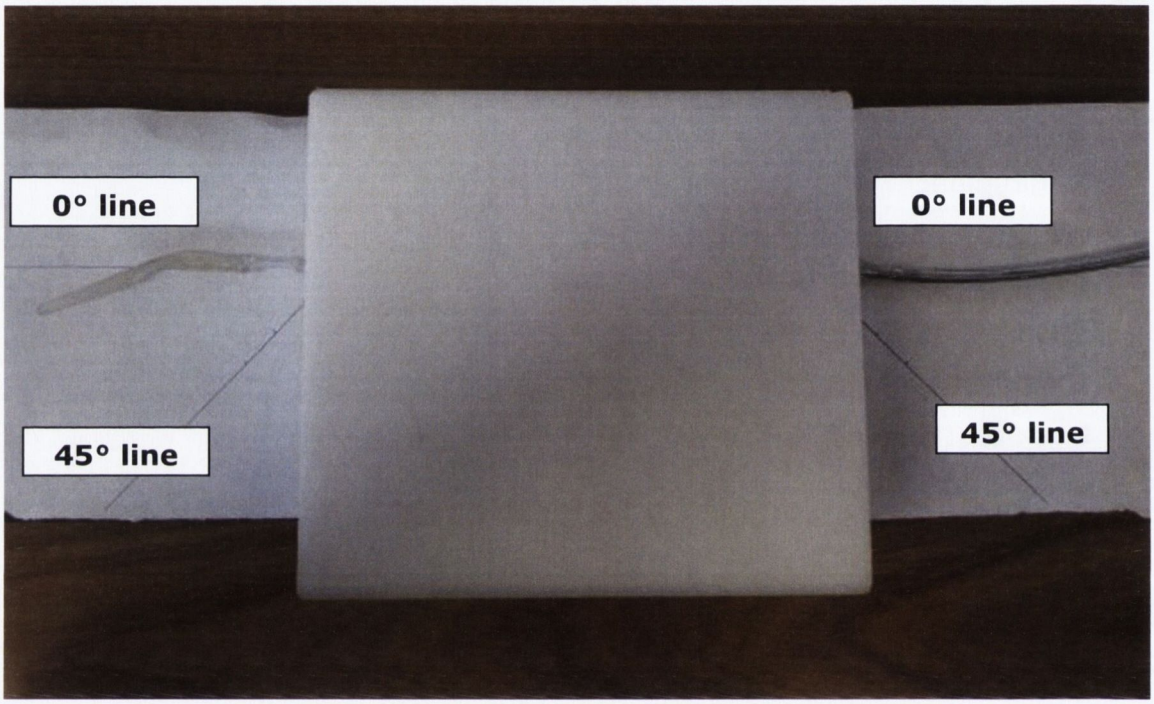

Figure 3.2 EndoFLIP® Balloon in the Diameter Measuring Block during Accuracy Testing

The ends of the balloon were held by hand 2cm away from the block on each side. This position was kept for ten seconds. The ends of the probe were then bent to the 45° line. This position was kept for ten seconds. The balloon was deflated and this procedure was repeated at a balloon pressure of 30mmHg ± 2mmHg. The balloon was deflated and the previous steps were repeated for the 9.80, 11.90 and 15.80mm diameter cavities.

3.2.1.3. Data Analysis

To analyse the data obtained during testing, the mean diameter (Dest) as measured by each electrode pair over each ten second measuring period was plotted. The EndoFLIP® unit samples at a frequency of 10Hz. Therefore, each electrode pair recorded one hundred diameter measurements (*n* =

100) over the course of each ten second measuring period and one hundred IBP measurements were also obtained.

For each cavity of the measurement block, the average profile for the 0° and 45° position of the EndoFLIP® balloon was plotted. The mean and standard deviation (SD) at each of the 16 diameter measures were included on each profile. For the reporting of standard deviation and mean values, the data was averaged for the sixteen diameter measurements for each individual experiment performed.

(ii) Balloon Constriction Test

The second accuracy test was designed to measure (i) the effect of sudden change in wall diameter and (ii) deviation of electrodes from the central longitudinal axis on accuracy of EndoFLIP® measures.

3.2.1.4. Equipment

The EndoFLIP® system and an EndoFLIP® probe were used for testing. Metal washers with specifications outlined in Table 3.1 were used to constrict the EndoFLIP® balloon probe. Each of the metal washers was measured with callipers a total of ten times. The mean and SD are reported in Table 3.1.

Table 3.1 Metal Washers used in Balloon Constriction Studies

Size	Internal diameter (mm) (SD)	External diameter (mm)(SD)	Longitudinal Thickness (mm)(SD)
M5	**5.57** ± .07	**9.85** ± 0.09	**1.05** ± 0.02
M6	**6.65** ± .06	**12.31** ± 0.11	**1.50** ± 0.03
M8	**8.44** ± .08	**16.62** ± 0.13	**1.08** ± 0.03

3.2.1.5. Procedure

On a piece of paper, a horizontal line of 15cm length was drawn with a mark at the midpoint. From this midpoint mark, three lines were drawn on each side at 15, 30 and 45° angles (see Figure 3.3). One M5 washer was placed around the balloon probe so that the washer was at the centre of the probe, between the eighth and ninth electrodes. The balloon was placed on

the 0° line with the washer at the midpoint mark and inflated to a 35ml volume. The balloon was then deflated and the procedure was repeated for the 15, 30 and 45° lines. The washer constriction was kept at the midpoint mark for each angle.

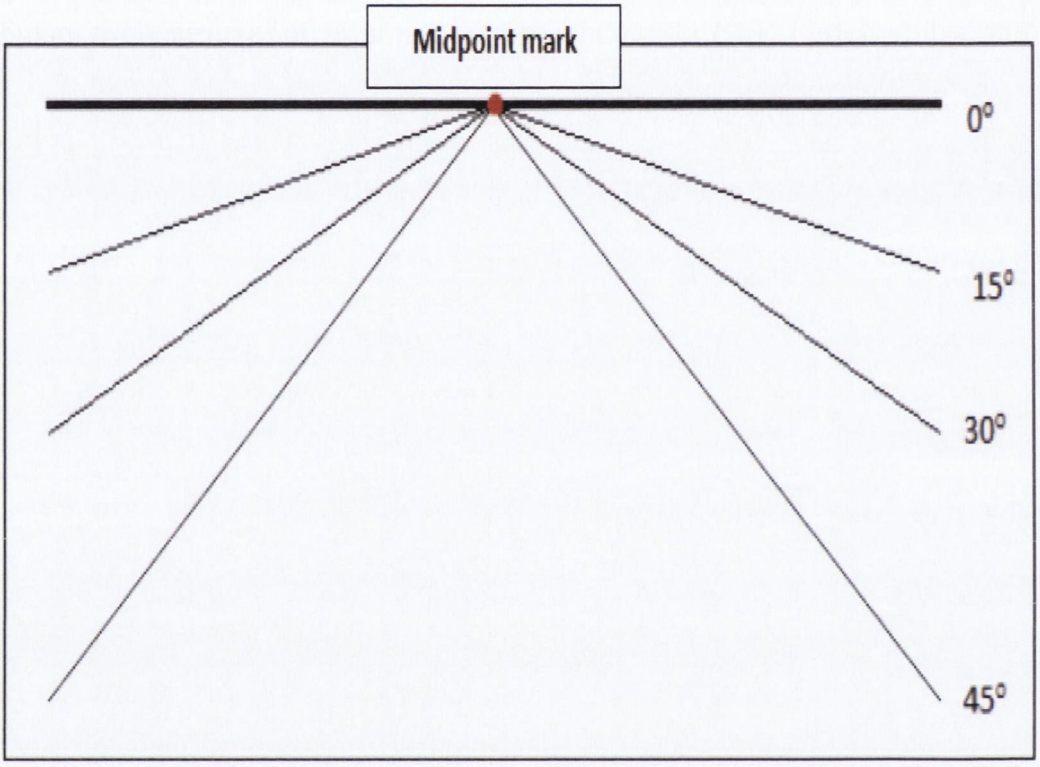

Figure 3.3 Outline of the angles used to bend the probe while constricted at the midpoint mark

With the balloon filled to 35ml, it was bent slowly from the 0° line to the 45° line over a time period of approximately ten seconds (Figure 3.4). Once this was completed, the procedure was repeated using one M6 washer and one M8 washer.

All of these steps were then repeated for three M5 washers, where the 3 washers were held together in order to extend the constriction in the longitudinal direction. This was repeated for two M6 washers, three M8 washers, five M5 washers, four M6 washers and five M8 washers.

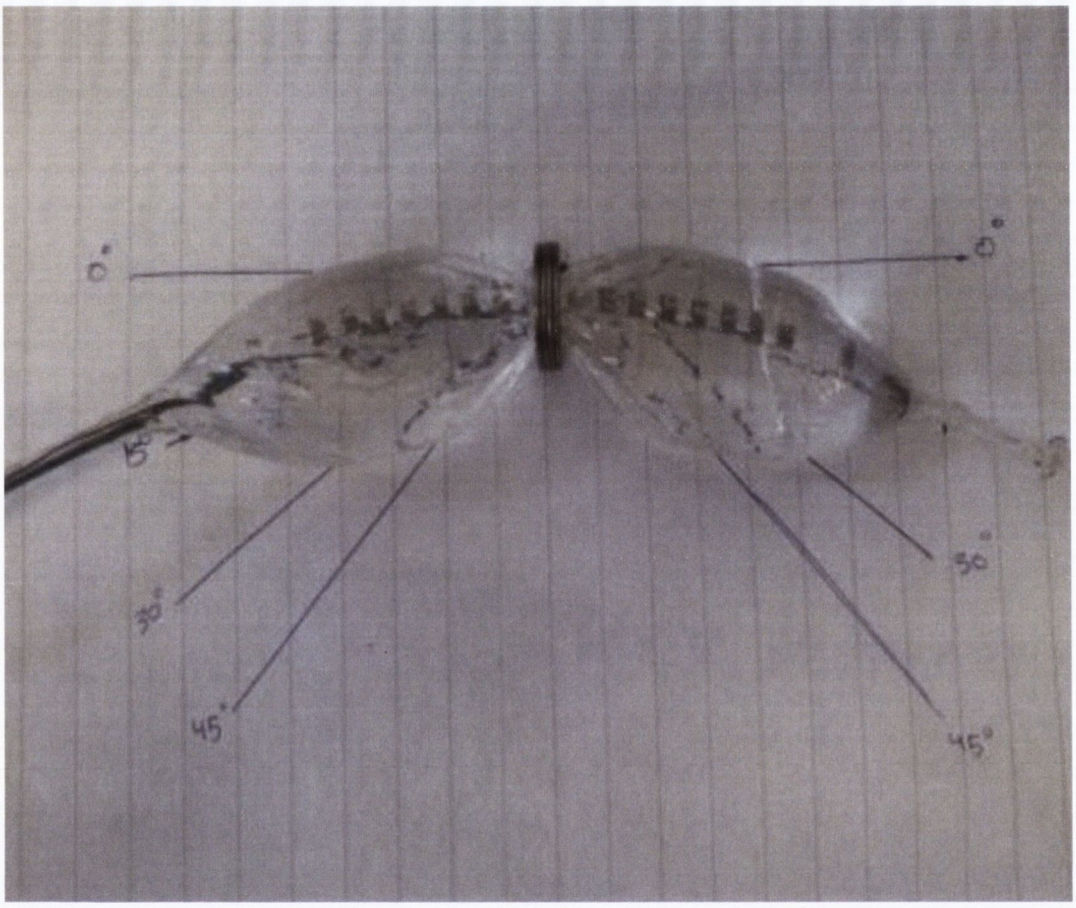

Figure 3.4 EndoFLIP® Balloon bent at 15° Angle during Accuracy Testing

3.2.1.6. Data analysis

The minimum diameter was plotted against the balloon volume between 25ml and 35 ml and the readings for the different angles for the different constriction thickness were compared. The minimum diameter was plotted against the angle while the balloon was being bent from 0 to 45 degree angles at a 35ml volume and the readings for the different constriction thickness were compared.

Next, methods to test the safety of inserting and positioning EndoFLIP® into the UOS in people with dysphagia under videofluoroscopy will be described.

3.2.2. Safe insertion and positioning of EndoFLIP® into the UOS in people with dysphagia

The hypotheses for this study were that (i) the EndoFLIP® could be safely inserted into the oesophagus without any serious adverse events; (2) the distended balloon could be positioned in the UOS and distended under VFS guidance until the hourglass shape of the UOS could be visualised on the EndoFLIP® screen and (iii) patients with dysphagia would be able to complete voluntary dry swallows and postural manoeuvres with the distended balloon in the UOS. Ethical approval for this study was obtained from St. James'/AMNCH Joint Research Ethics Committee (JREC) (see Chapter 3.1 and Appendix 4).

3.2.2.1. Participants

Two males with oro-pharyngeal dysphagia were recruited by the researcher for pilot studies to insert EndoFLIP® under VFS. The first subject was a 67 year old male with a medical history of stroke, hypertension, type 2 diabetes and gastritis. He had mild oro-pharyngeal dysphagia. The second subject was an 85 year old male with a medical history of recurrent lower respiratory tract infections (LRTIs), atrial fibrillation and hypertension. He also presented with mild oro-pharyngeal dysphagia.

3.2.2.2. Equipment

EndoFLIP® Device

A commercially developed FLIP (EndoFLIP® system, Crospon Ltd., Galway, Ireland) was used (Figure 3.5A). EndoFLIP® is Conformité Européenne (CE) marked under the European Device Directive and has been approved for inflation in the oesophagus. The EndoFLIP® system is pressure limited. The upper limit was set at 80mmHg based on pilot studies. If this set pressure limit is reached, the system will stop the inflation and the alarm will sound.

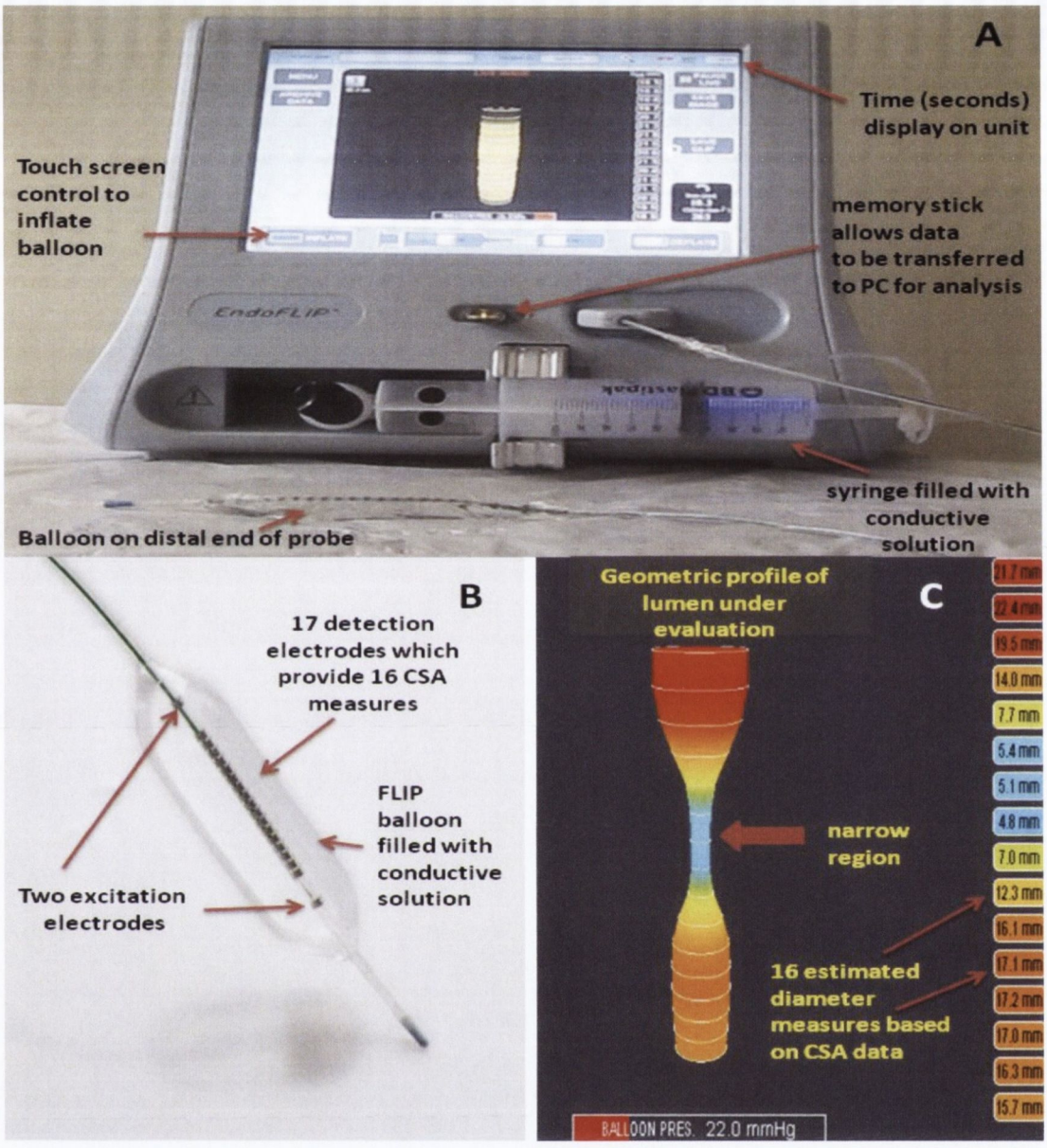

Figure 3.5 EndoFLIP® System[16]

A) EndoFLIP® system comprising recording unit, syringe and probe. Syringe is filled with conductive solution. Probe is connected to unit and syringe. Touch screen control on monitor used to inflate or deflate balloon on distal end of probe.

B) Balloon at distal end of EndoFLIP® probe. Once balloon is positioned to straddle the UOS, it is inflated with 12 or 15ml of conductive solution. Two excitation electrodes emit an electrical current which allows 17 detection electrodes to provide 16 adjacent diameter measurements within the UOS.

C) EndoFLIP® balloon positioned in the UOS

D) Geometric profile of the UOS as seen in real-time on EndoFLIP® screen during UOS evaluation. Note sixteen diameter measurements on right hand side and measure of IBP at bottom of screen. The screen was monitored during evaluation to ensure balloon remained in position.

EndoFLIP® Balloon Design

The original EndoFLIP® balloon was employed for evaluations. This balloon is made of polyutherane material. It has a maximum volume of 60 ml and is mounted on the distal 14 cm of a probe (EF-325) (length 240cm, diameter 25mm) attached to the EndoFLIP® unit (Figure 3.5B). This balloon assumes a 10cm long cylindrical shape with maximum diameter of 2.5 cm. The maximum balloon diameter was critical to prevent airway compromise during balloon distension. Across a 7.5cm segment within the balloon, 17 ring electrodes were spaced 5mm apart to obtain 16 impedance planimetry measurements (Figure 3.6). Given the length of the UOS described in the literature review (Chapter 2.2.1), this balloon length would allow diameter and pressure changes above (i.e., pharynx) and below (i.e., upper oesophagus) the UOS to be captured and for UOS opening to be observed despite its upward shift during swallowing. Excitation electrodes situated at either end of the 17 ring electrodes emitted a constant low electrical current within the balloon. The probe also contained a solid-state pressure transducer to measure IBP.

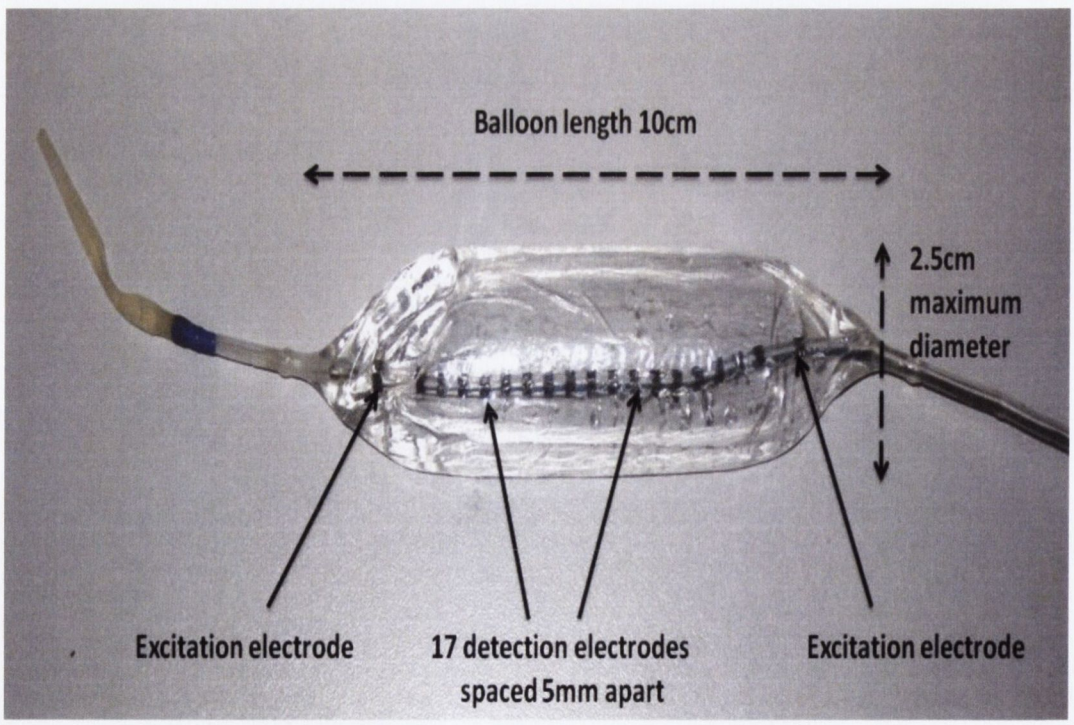

Figure 3.6 Original EndoFLIP® Balloon

3.2.2.3. Protocol

As per requirements of the local ethics committee, a member of Tallaght Hospital Radiology team was present for insertion of the EndoFLIP® probe. The EndoFLIP® system was positioned beside the subjects who were seated upright on a chair within the Radiology suite, Tallaght Hospital, Dublin. The equipment was powered on and both the syringe and a pre-calibrated probe were connected to the EndoFLIP® unit. An automated purge sequence initiated by the EndoFLIP® removed air from the balloon and calibrated the pressure measurement inside. Topical anaesthesia (Lignocaine spray) was administered to the nares. The tip of the EndoFLIP® probe was lubricated and inserted trans-nasally by the researcher until the deflated balloon at the distal end of EndoFLIP® was judged to have passed into the proximal oesophagus (30cm marking on EndoFLIP® catheter). The subjects were seated in a 90 degree angle upright position. The EndoFLIP® catheter was held outside of the nares by an assistant to minimize balloon displacement during the evaluation. The protocol for balloon distensions is depicted in Figure 3.7. Participants were also asked to perform a dry swallow and head turn as these postures are typically used in dysphagia evaluations and it was important to determine the safety and positioning of EndoFLIP® balloon during these manoeuvres.

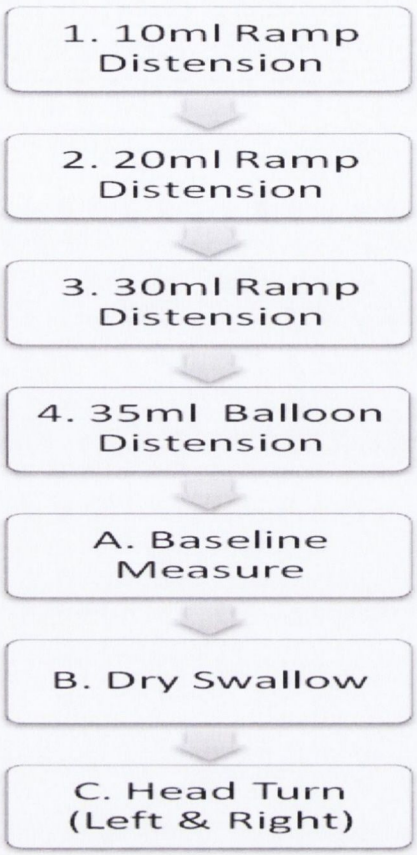

Figure 3.7 Study Protocol for Pilot Balloon Placement Studies under Videofluoroscopy

3.2.2.4. Validation Tool: Videofluoroscopy

VFS was used as a validation tool for these studies (see full description of this tool in Chapter 2.5.2.1). VFS was conducted using a Siemens AXIOM Artis dMP multipurpose C-arm X-ray system with dynamic flat detector (30 cm 9 40 cm). Images were recorded for later slow motion and millisecond frame-by-frame analysis (frame rate = 25 frames/s) using a Video South Panasonic DVC Pro digital video recorder and 14-inch high-resolution monitor and a high-quality clip-on microphone. The procedures were recorded onto a Panasonic DVC Pro 66L AJ-P66LP videotape. During the radiographic study, subjects were instructed by the researcher to sit on a standard chair while lateral plane views were recorded. The fluoroscopic tube was focused on the lips anteriorly, the pharyngeal wall and the cervical vertebrae posteriorly, the hard palate superiorly and the bifurcation of the airway and the oesophagus inferiorly.

3.2.3. Safe insertion and positioning of EndoFLIP® into the UOS in healthy adults without videofluoroscopic guidance

The previous study (Chapter 3.2.2) employed VFS to safely and accurately position the EndoFLIP® balloon in the UOS. It was important to determine if VFS was necessary for further guidance. For this sub-question, the researcher hypothesised that (i) EndoFLIP® could be safely and accurately inserted and positioned in the UOS without VFS guidance; (ii) subjects would be able to safely perform swallows and postural manoeuvres commonly employed in clinical practice with the distended EndoFLIP® balloon in position in the UOS and (iii) preliminary temporal, diameter and IBP data relating to the UOS could be acquired. Ethical approval was obtained from the Research Ethics Committee, University Hospitals Leuven, Belgium and from St. James'/AMNCH Joint Research Ethics Committee (JREC) (see Chapter 3.1 and Appendix 4).

3.2.3.1. Participants

This study was undertaken at a Neurogastroenterology Clinic in University Hospitals Leuven, Belgium. Subjects were recruited from a pool of healthy volunteers over a one day period in a Neurogastroenterology Clinic in University Hospitals Leuven, Belgium. Inclusion criteria were; (1) no history of oro-pharyngeal or oesophageal dysphagia, (2) no history of gastrointestinal, neurological or respiratory disease (3) no history of head and neck cancer or ear nose and throat conditions. Five healthy adults (one male), with a mean age of 36 years (range 20-48; standard deviation (SD) 10.5) met inclusion criteria. Written consent was obtained from subjects. Before each EndoFLIP® evaluation, all voluntary swallowing manoeuvres included in the study protocol were explained and demonstrated to subjects by the researcher.

3.2.3.2. Protocol

As per requirements of the local ethics committee, a member of University Hospitals Leuven, Belgium Gastroenterology team was present for insertion of the EndoFLIP® probe. The EndoFLIP® system was positioned beside the

subject who was seated upright on a chair within the clinic room (Neurogastroenterology & Motility Clinic, University Hospital Leuven). The equipment was powered on and both the syringe and a pre-calibrated probe were connected to the EndoFLIP® unit. An automated purge sequence initiated by the EndoFLIP® removed air from the balloon and calibrated the pressure measurement inside. Topical anaesthesia (Lignocaine spray) was administered to the posterior pharyngeal wall and subjects were instructed to perform a dry swallow. The tip of the EndoFLIP® probe was lubricated and inserted orally by a member of the research team until the deflated balloon at the distal end of EndoFLIP® was judged to have passed into the proximal oesophagus (30cm marking on EndoFLIP® catheter). The subject was transferred to a bed and seated in a 90 degree angle upright position. The EndoFLIP® catheter was held outside of the subjects' teeth by an assistant to minimize displacement during the evaluation.

When the subject became accustomed to the probe, the probe balloon within the oesophagus was distended with 10mls saline solution from the syringe using a touch screen function on the EndoFLIP® monitor. The inflated balloon was then slowly retracted by the researcher until the hourglass shape of the UOS could be visualised on the EndoFLIP® display (17-20cm marking on EndoFLIP® catheter). This confirmed the balloon position in the UOS. While holding the catheter in place, the balloon was deflated by pressing the touch screen control on the unit monitor.

UOS Distensibility Testing

After a brief habituation period of 1-2 minutes, two ramp distensions to 20ml were completed (rate 60ml/minute) by the researcher. Subjects were requested not to swallow during distensions and the EndoFLIP® screen was monitored to ensure the balloon remained in position. Two distensions were completed to allow for an accommodation effect.

UOS Opening during Swallowing Testing

Once the distensibility testing was completed, the balloon was inflated with 15mls conductive solution. Of note, after two pilot volunteer studies, this 15ml balloon volume was reduced to a 12ml balloon volume to optimise

tolerance levels as two subjects were noted to have difficulty tolerating the balloon distended with 15mls in the UOS during swallow trials. Once a baseline measure of minimum UOS diameter (mm) and IBP (mmHg) was recorded, subjects were asked by the researcher to complete the following:

(a) dry swallow;
(b) 5ml liquid swallow delivered orally via a syringe; and
(c) voluntary swallow manoeuvres during 5ml liquid swallows delivered orally via syringe: (i) swallow with head turn to left; (ii) swallow with head turn to right; (iii) swallow with chin tuck; (iv) effortful swallow; (v) swallow with Mendelsohn manoeuvre and (vi) supraglottic swallow. The time (in seconds) displayed on the EndoFLIP® device at the execution of each swallow was recorded.

3.2.3.3. Data Analysis

As this was a pilot study, descriptive statistics were employed to analyse data. Mean CSA and IBP were determined across 1, 5, 10, 15 and 20ml balloon volumes during distension testing. During dry and liquid swallowing, mean UOS diameter and minimum IBP measures were established.

3.3. Research Question 2: Can EndoFLIP® provide normative data on UOS distensibility and UOS opening during swallowing in an adult healthy group?

The four sub-questions and associated alternative hypotheses for this study were:

(a) UOS distensibility in an adult healthy group using EndoFLIP®

The hypothesis was that, due to the high tone of the UOS, UOS CSA would stop increasing significantly during distensibility testing and IBP would increase significantly during balloon distension.

(b) UOS opening during swallowing in an adult healthy group using EndoFLIP® and creation of colour contour plots of swallowing

It was hypothesised that UOS diameter would increase significantly during dry and liquid swallowing and duration of UOS opening could be captured during swallow events. In addition, IBP would decrease significantly during dry and liquid swallowing. It was also hypothesised that an increase in extent and duration of UOS opening and in drop in IBP would be observed with increasing bolus volumes and that EndoFLIP® data could be used to create colour contour plots of swallowing measures.

(c) Gender differences in EndoFLIP® measures of UOS distensibility and UOS opening during swallowing in an adult healthy group

The hypothesis was that statistically significant differences in CSA and IBP would be observed across 1, 5, 10, 15 and 20ml balloon volumes during ramp distensions and statistically significant differences in UOS diameter, duration of UOS opening and minimum IBP would be observed across genders during swallowing across bolus volumes.

(d) EndoFLIP® evaluation of postures and manoeuvres to improve UOS opening during swallowing in an adult healthy group

It was hypothesised that voluntary postures and manoeuvres commonly employed in dysphagia practice (chin tuck, head turn left and right, effortful swallow, Mendelsohn manoeuvre, supraglottic swallow) would alter the extent and duration of UOS opening during swallowing events and alter drop in IBP at rest and during dry, 5ml and 10ml liquid swallowing in an adult healthy group.

Ethical approval was obtained from the Research Ethics Committee, University Hospitals Leuven, Belgium and from St. James'/AMNCH Joint Research Ethics Committee (JREC) (see Appendix 4).

3.3.1. Participants

For this second key research question, the study was undertaken in a Neurogastroenterology Clinic in University Hospitals Leuven, Belgium and all subjects were prospectively evaluated over a two day period. The same inclusion and exclusion criteria employed in pilot studies were employed (see Chapter 3.2.3.1). Fourteen subjects (six males, eight females) with a mean age of 30 years (age range 20-50 years; SD=11.02) met inclusion criteria for this study (Table 3.2). Written consent was obtained from all subjects by the researcher.

Table 3.2 Subject Demographics

Subject	Initials	Age	Gender	Height (cm)	Weight (kg)
1	KB	28	F	163	58
2	RG	50	F	161	56
3	VD	24	M	194	107
4	SB	20	F	165	76
5	CC	48	F	170	66
6	AR	28	F	159	52
7	RS	23	M	179	65
8	GH	33	M	184	95
9	JD	50	M	179	70
10	JR	33	F	174	60
11	NW	23	F	176	64

12	TV	24	M	193	83
13	CC	21	F	169	53
14	KD	21	M	183	71

3.3.2. Protocol

(A) UOS Distensibility

For normative data studies, the EndoFLIP® probe was inserted orally (Figure 3.8) and positioned in the UOS by a member of the research team according to the protocol already described in Chapter 3.2.3.2 (Figure 3.9). As per the requirements of the local ethics committee, a member of University Hospitals Leuven, Belgium Gastroenterology team was present for insertion of the EndoFLIP® probe. UOS distensibility testing was completed by the researcher as described already in Chapter 3.2.3.2.

(B) UOS Opening during Swallowing

When distensibility testing was completed, the balloon remained in the UOS and was inflated with 12mls conductive solution. A baseline measure of minimum UOS diameter (mm) and IBP (mmHg) was recorded. Subjects were then asked by the researcher to complete the following:

(a) two dry swallows
(b) two 5ml liquid swallows delivered orally via a syringe
(c) two 10ml liquid swallows delivered orally by a syringe.

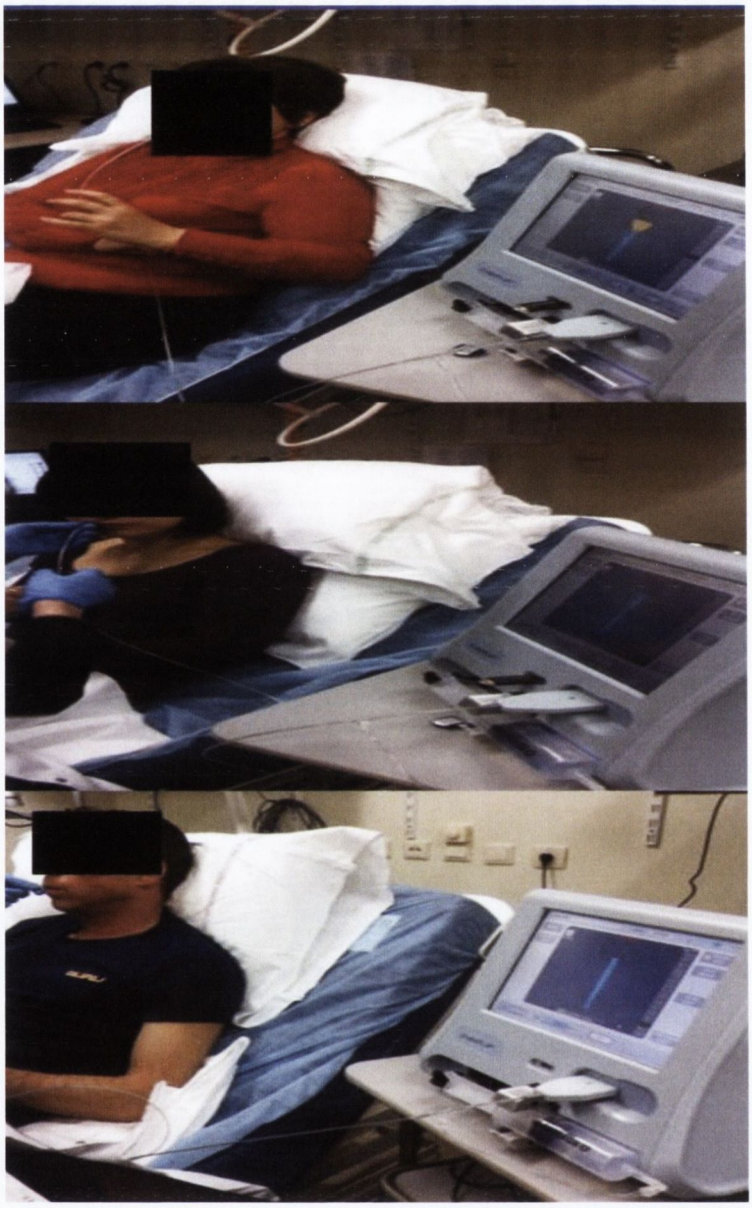

Figure 3.8 Oral Insertion of EndoFLIP® probe during Studies

A minimum 10 second time period between the performances of each swallow was enforced by the researcher to easily identify swallow events during data analysis. The time (in seconds) displayed on the EndoFLIP® device at the execution of each swallow was recorded.

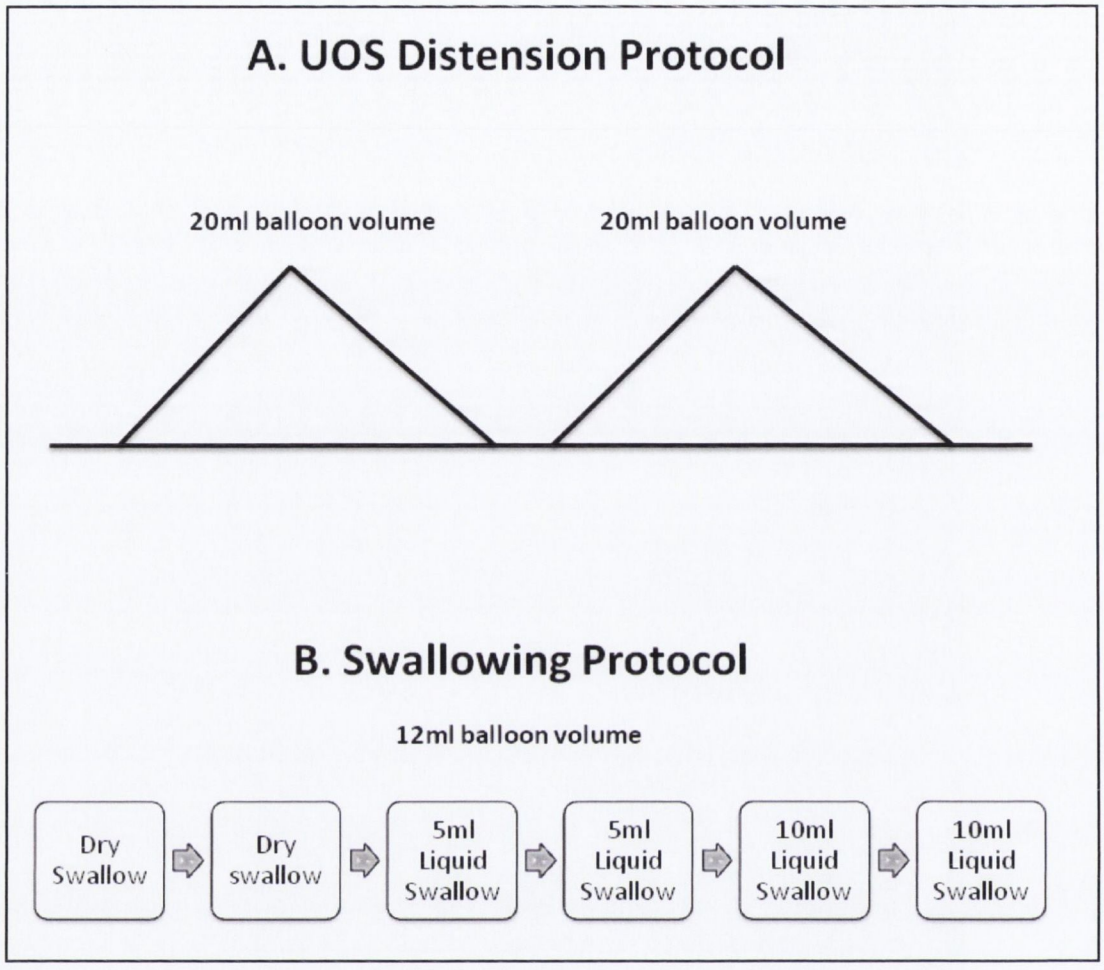

Figure 3.9 Study Protocol for EndoFLIP® Evaluation of the UOS[17]

(C) Gender Differences in UOS Measures

Protocols for UOS distensibility and UOS opening during swallowing provided data to determine gender differences in UOS distensibility and UOS opening during swallowing.

[17] A. Two ramp distensions to 20ml balloon volume will be performed. During data analysis, CSA and IBP data will be extracted from the second ramp distension to establish UOS distensibility. This is to cater for a potential habituation effect within the UOS.
B. Subjects will be asked to execute two dry swallows and two 5ml and 10ml liquid swallows. A minimum time period of ten seconds will be enforced between swallows to easily identify swallow events during data analysis. To address a potential habituation effect, data will be extracted from the second dry, 5ml and 10ml liquid swallows.

(D) Effect of Postures and Manoeuvres on UOS Opening

Once distensibility and UOS opening during swallowing protocols were completed (Figure 3.9), the same group of healthy adult subjects were evaluated to determine the effects of postures and manoeuvres on UOS opening during swallowing. With the balloon in position in the UOS and filled with 12ml saline solution, subjects were instructed by the researcher to complete; (i) two dry swallows, (ii) two 5ml liquid swallows and (iii) two 10ml liquid swallows across six different conditions; (a) chin tuck, (b) head turn right, (c) head turn left, (d) effortful swallow, (e) Mendelsohn manoeuvre and (f) supraglottic swallow (see Figure 3.10). Before each EndoFLIP® evaluation, all voluntary postures and manoeuvres included in the study protocol had been thoroughly explained and demonstrated to subjects (Table 3.3).

Table 3.3 Instructions to Subjects for Execution of Postures and Manoeuvres

	Posture/Manoeuvre	Instruction to Participant
1	Chin tuck	Take the water into your mouth. Tuck your chin down all the way towards your chest and swallow.
2 & 3	Head turn right and left	Take the water into your mouth. Turn your head ninety degrees to indicated side without turning your shoulders. Now swallow.
4	Effortful swallow	Take the water into your mouth. Keep your lips tightly together. Perform a strong, hard swallow.
5	Mendelsohn manoeuvre	Place your fingers under your chin to feel your Adams' apple. Take the water into your mouth. During swallowing, feel your Adams' apple slide upwards. Try to keep your Adams' apple in that position as high as you can for as long as possible.
6	Supraglottic swallow	Take the water into your mouth. Take a deep breath through your nose. Hold your breath tight. Bear down and swallow hard. Exhale forcefully after swallowing

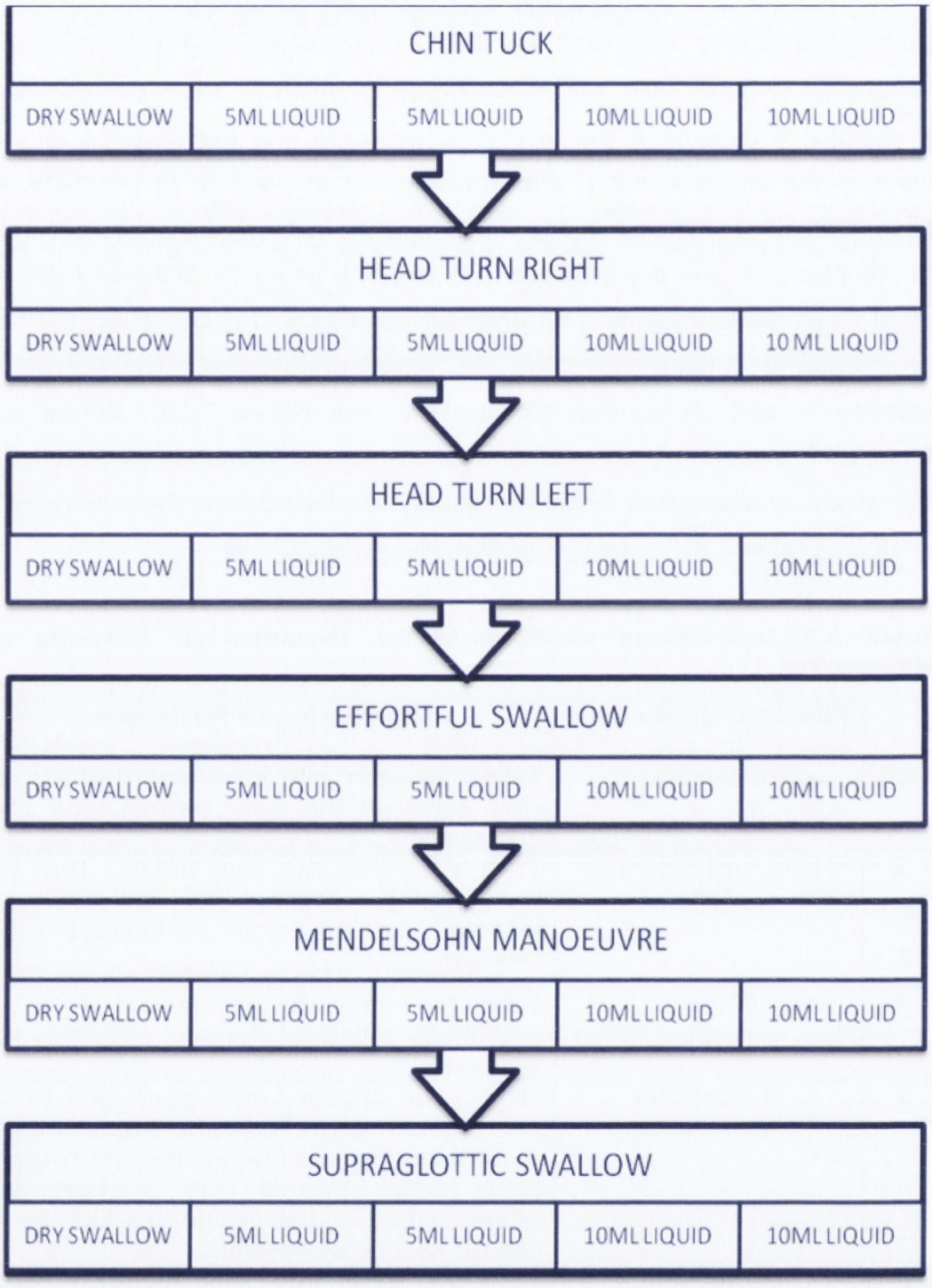

Figure 3.10 Study Protocol to Evaluate Effects of Postures and Manoeuvres

A minimum 10 second time period was enforced between the performances of each swallow to easily identify swallow events during data analysis. The time (in seconds) displayed on the EndoFLIP® device at the execution of each swallow was recorded. When the protocol was completed, 12mls was deflated from the balloon and the probe was removed. When this protocol was completed, the balloon was deflated and the probe was removed. A data collection form was developed and used for this entire protocol (Appendix 5).

3.3.3. Data Analysis

(A) UOS Distensibility

EndoFLIP® provides sixteen measures of CSA (mm^2) and a measure of IBP (mmHg) at a rate of ten hertz (Hz) during distensions. To cater for a habituation effect, data from the second 20ml ramp distension was transferred from EndoFLIP® into an Excel document on a personal computer. CSA (mm^2) and IBP (mmHg) measures were determined at 1, 5, 10, 15 & 20ml balloon volumes across subjects.

(B) UOS Opening during Swallowing

EndoFLIP® measures of diameter, IBP and time were transferred into an Excel document. To determine change in UOS opening during swallowing, three EndoFLIP® measures were selected for examination at rest and during swallow events. These measures were (i) extent of UOS opening (mm); (ii) duration of UOS opening (secs); and (iii) minimum IBP (mmHg) (Figure 3.11). These three outcome measures are defined below.

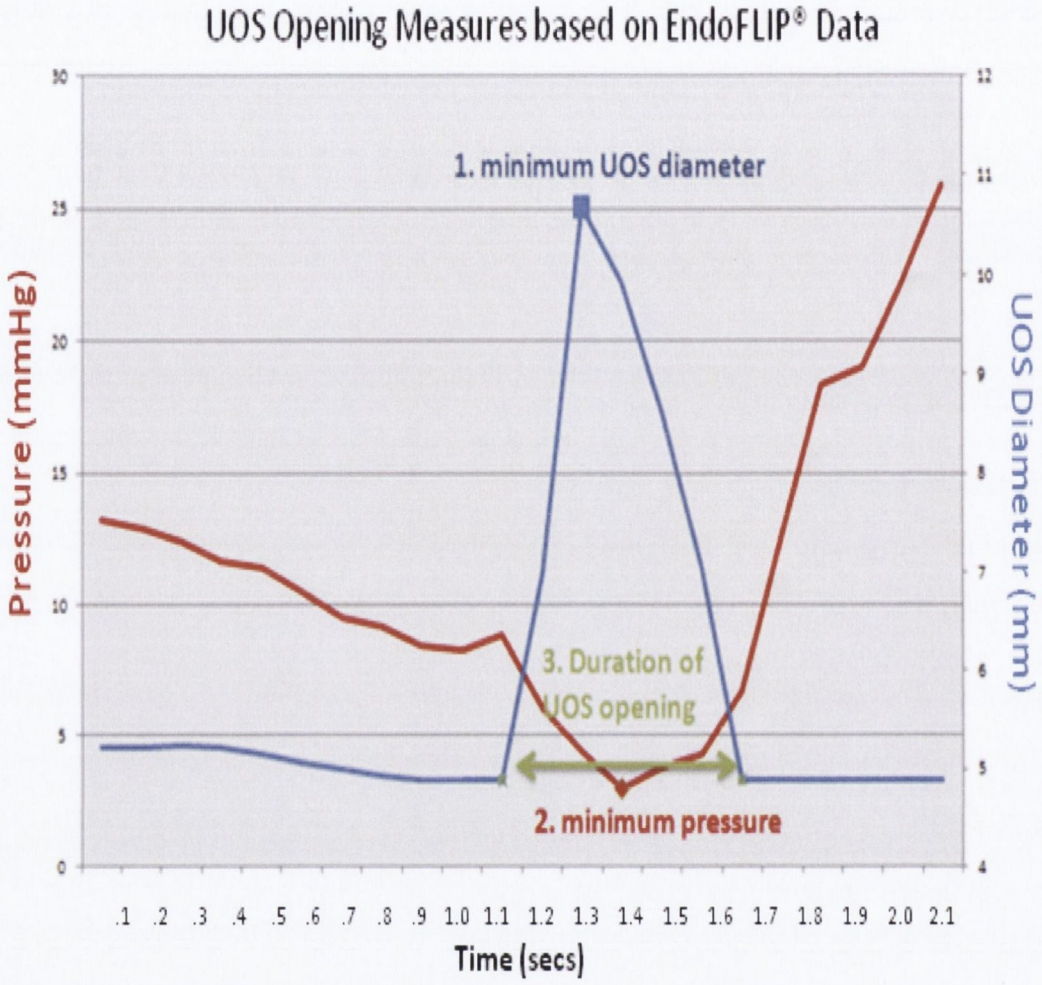

Figure 3.11 Outcome Measures for Swallowing based on EndoFLIP® Data

(i) **Extent of UOS Opening:** EndoFLIP® provides sixteen estimated diameter (mm) measurements (based on CSA) at a rate of ten per second throughout the examination. The minimum of the sixteen diameter measures at each time point is considered to be the narrow UOS region (Figure 3.11). This minimum UOS diameter measure was evaluated during swallow events to ascertain the extent of UOS opening during swallowing. Of note, the minimal detectable diameter of the EndoFLIP® probe is 4.8mm (or 18.1mm2) because of its physical size.

(ii) **Duration of UOS opening (ms):** Sixteen diameter measures are provided by EndoFLIP® at a rate of ten per second. Duration of UOS opening is defined as the time from which the narrowest diameter in the UOS region sharply rises from its baseline during swallowing until its return to baseline diameter (Figure 3.11).

(iii) **Minimum IBP:** EndoFLIP® provides ten measures of IBP (mmHg) per second. To examine change in IBP observed during swallow events, the minimum IBP measurement during swallowing was examined across swallows (Figure 3.11).

Initially, EndoFLIP® diameter, pressure and time measurements at rest and during swallowing were inputted into Excel to create colour plots. This prompted the use of OriginPro software to display diameter and pressure data derived from EndoFLIP® at rest and during swallowing in colour contour plots. Plots are presented within the results chapter (Chapter 4).

(C) Gender Differences in UOS Measures

Measures of UOS opening during swallowing were obtained for all subjects as described in Chapter 3.3.3. Male subject data (n=6) was compared to data from females (n=8).

(D) Effect of Postures & Manoeuvres on UOS Opening

Within each subject's protocol, data from one dry swallow and from two 5ml and 10ml liquid swallows across all seven conditions was included in data analysis (i.e., 385 swallows) (Figure 3.10). In order to quantify the effects of postures and manoeuvres on UOS opening during swallowing, measures of extent and duration of UOS opening during swallowing and minimum drop in IBP were calculated across swallows (see Chapter 3.3.3).

3.3.4. Statistical Analysis

(A) UOS Distensibility

Data was entered by the researcher into SPSS statistical software package (version 19j (IBM CORP, New York, U.S.A.). Based on Shapiro-Walk tests, all data was not normally distributed. Data was therefore expressed as medians (interquartile range (IQR)) and non-parametric tests were employed. Kruskal-Wallis tests were used to determine a change in UOS CSA and IBP across balloon volumes (1, 5, 10, 15 and 20mls) during distensibility testing. Significance was set at $P<.05$. Where significance was found, multiple comparisons were made using the Wilcoxon rank sum test. Bonferroni correction was made and post-hoc tests were significant at an adjusted alpha level of 0.0127. Wilcoxon signed rank tests were used to establish a gender difference in median CSA and IBP measures at 1, 5, 10, 15 and 20 ml balloon volumes during distensibility testing.

(B) UOS Opening during Swallowing

Kruskal-Wallis tests were also used to establish differences in UOS diameter, IBP and duration of UOS opening at baseline and across second dry, 5ml and 10ml liquid swallow events (second swallows of each volume were selected to cater for a habituation effect). A P $<.05$ indicated statistical significance. Where significance was found, multiple comparisons were made using the Wilcoxon rank sum test. Bonferroni correction was used to determine if the post-hoc tests were significant and an adjusted alpha of 0.008 was used. Wilcoxon signed rank tests were used to establish a gender difference in median diameter and IBP measures during dry, 5ml and 10ml liquid swallows.

(C) Gender differences in UOS Measures

Wilcoxon signed rank tests were used to establish a gender difference in median diameter, duration and IBP measures during dry, 5ml and 10ml liquid swallows.

(D) Effect of Postures & Manoeuvres on UOS Opening

For this analysis, data was entered into SAS statistical software package. Based on Shapiro-Wilk tests, data was normally distributed. Data was therefore expressed as means and a mixed model analysis was performed. A p <.05 indicated statistical significance. A trend towards significance was defined as a p value between 0.05-0.1. Where significance was found, post-hoc tests were completed with Dunnett adjustment.

3.4. Research Question 3: How do EndoFLIP® measures of UOS opening during swallowing compare to an existing dysphagia evaluation such as High Resolution Manometry with Impedance?

In this study, the researcher hypothesised that EndoFLIP® temporal, diameter and pressure measures of UOS opening during swallowing would significantly correlate with data obtained from AIM analysis using combined HRM-MII in a group of healthy adults. This study was also conducted in University Hospital Leuven, Belgium and involved HRM-MII as a reference standard tool for EndoFLIP®. Ethical approval was obtained from the Research Ethics Committee, University Hospitals Leuven, Belgium and from St. James'/AMNCH Joint Research Ethics Committee (JREC) (see Appendix 4).

3.4.1. Participants

Data from eleven of the fourteen subjects recruited at this clinic site and who participated in previous studies (see Chapter 3.3.1) was included for analysis in postural strategies studies. Data from only eleven subjects was analysed as just eleven of the fourteen subjects recruited also attended for HRM-MII evaluation. The eleven subjects included (six males, five females) had a mean age of 30 years (age range 20-50 years; SD=11.02). Written consent was obtained from all subjects. For all subjects, the EndoFLIP® evaluation and a combined HRM-MII study was performed on the same day. The time span between procedures was minimised to ensure subjects' presentation did not differ across evaluations.

3.4.2. Protocol

A separate researcher (NR), who was not present for EndoFLIP® testing and was blinded to EndoFLIP® findings, completed the combined HRM-MII test on the healthy adult subjects in a separate clinic room (Neurogastroenterology & Motility Clinic, University Hospital Leuven) on the same day as EndoFLIP® testing. For the AIM analysis study, a 3.2mm diameter solid state manometric and impedance catheter incorporating 25

1cm-spaced pressure sensors and 12 adjoining impedance segments, each of 2 cm (Unisensor USA Inc, Portsmouth, NH) was used.

Subjects were intubated after topical anaesthesia (Lignocaine spray) and the catheter was positioned with sensors straddling the entire pharyngo-oesophageal segment (velo-pharynx to proximal oesophagus). Pressure and impedance data was acquired at 20Hz (Solar GI acquisition system, MMS, The Netherlands) with the subject sitting upright. All bolus stock contained 1% NaCl to enhance conductivity. All subjects were tested with dry and 5 and 10ml liquid boluses as measured and delivered orally via a syringe.

3.4.3. Data Analysis

One researcher (NR), who was blinded to EndoFLIP® results, analysed HRM-MII data. These measures were inputted into Excel alongside EndoFLIP® measures for corresponding swallow events to allow for comparison of data. AIM analysis parameters are defined in Table 3.4. For a comprehensive review regarding the acquisition of AIM analysis parameters, see Chapter 2.5.5.4 in the literature review.

Table 3.4 Definitions of Parameters derived from EndoFLIP® and AIM Analysis

EndoFLIP® Parameters	**UOS Diameter (mm)**	Minimum UOS diameter was evaluated during swallow events to ascertain the extent of UOS opening during swallowing.
	UOS Opening Duration (ms)	Time from which the narrowest diameter in the UOS region sharply rises from its baseline during swallowing until its return to baseline diameter.
	Min IBP (mmHg)	Minimum intra-balloon pressure measurement during swallowing.
AIM analysis Parameters	**PeakP**	Mean pressure of the entire pharyngeal stripping wave.
	PNadImp	Mean pressure at the time when pharyngeal impedance is at nadir.
	TNadImp-PeakP	Mean time from nadir impedance to peak pressure.
	Flow Interval	Time interval of impedance drop.
	Swallow Risk Index	Analysis evaluating the pattern of change in four pharyngeal pressure-flow swallow variables in relation to the occurrence of aspiration.
	UOS RI	UOS relaxation interval.
	UOS NadP	UOS nadir relaxation pressure.
	UOS IBP	Intra-bolus pressure.
	UOS Resistance	Intra-bolus pressure/relaxation interval.

3.4.4. Statistical Analysis

Statistical analysis was completed using SAS statistical software (249). Initially, EndoFLIP® and HRM-MII parameters were correlated per volume (dry, 5ml and 10ml) using Spearman's Rho (non-parametric) to establish trends in the data (rho =0.4 & p values 0.05). Any statistically significant correlations identified were included in a series of mixed mode analysis regressions performed within the SAS software to investigate the association between EndoFLIP® and AIM analysis measures.

Methods addressing the fourth key research question, which focused on the clinical utility of EndoFLIP® in dysphagia practice, are described next.

3.5. Research Question 4: What is the clinical utility of EndoFLIP® in dysphagia practice?

To address this fourth research question, two sub-questions needed to be addressed. The methodologies for these studies are described below.

3.5.1. Clinical utility of EndoFLIP® in a population of people with known UOS dysfunction

Based on the literature review which described weak POS tone post total laryngectomy surgery (Chapter 2.3.6), the alternative hypotheses for this study were that (i) there would be a statistically significant increase in POS CSA during distensibility testing whereas IBP would not increase significantly; (ii) during dry and liquid swallowing, POS diameter would increase significantly from baseline and IBP would decrease significantly; (iii) statistically significant differences in CSA and IBP would be observed during distensibility testing between the total laryngectomy group and healthy controls and (iv) statistically significant differences in extent and duration of sphincter opening and in minimum IBP during swallowing would be observed between the total laryngectomy group and healthy controls. Ethical approval was obtained from St. James'/AMNCH Joint Research Ethics Committee (JREC) (see Appendix 4).

3.5.1.1. Participants

Patients with total laryngectomy were recruited by the researcher over a three month period in a weekly outpatient ENT clinic in an acute hospital setting at St. James' Hospital, Dublin, Ireland. The one inclusion criterion was a history of total laryngectomy surgery (with or without associated pharyngectomy, oesophagectomy or radical neck dissection) secondary to head and neck cancer. Exclusion criteria included a history of Zenker's diverticulum to ensure safe insertion of the EndoFLIP® probe and safe distension of the balloon in the POS region. Ten subjects (seven males, three females) with a mean age of 67 years (age range 61-75 years) met inclusion criteria and provided informed consent (Table 3.5). Distensibility and POS opening findings from the laryngectomy group were compared to

data obtained from a control group of thirteen healthy adults previously studied (refer to Chapter 3.3.1).

Table 3.5 Subject Demographics

Laryngectomy Group (n=10)			Healthy Controls (n=14)		
Subject	**Age**	**Gender**	**Subject**	**Age**	**Gender**
1	61	F	1	28	F
2	66	F	2	50	F
3	69	M	3	24	M
4	75	M	4	20	F
5	68	M	5	48	F
6	62	M	6	28	F
7	64	M	7	23	M
8	75	M	8	33	M
9	70	F	9	50	M
10	63	M	10	33	F
			11	23	F
			12	24	M
			13	21	F
			14	21	M

3.5.1.2. Protocol

The same study protocols for distensibility and UOS opening during swallowing described above (Chapter 3.3.2) were completed in adults with total laryngectomy. However, two deviations from the previous study protocol existed. These were:

1. Data collection for clinical studies was conducted in an ENT outpatient clinic in St. James' Hospital, Dublin, Ireland. As per ethical approval, a member of St. James' ENT Surgical team was present for each insertion of the EndoFLIP® probe.
2. The EndoFLIP® probe was passed trans-nasally by the researcher during clinical studies. Topical anaesthesia (Lignocaine spray) had already been administered to the nares of patients during a preceding routine ENT examination. As a result, the tip of the EndoFLIP® probe was lubricated and inserted trans-nasally by a member of the research team until the balloon at the distal end of

EndoFLIP® was judged to have passed into the proximal oesophagus (30cm marking on EndoFLIP® catheter). The EndoFLIP® catheter was held at the nares by a researcher to minimize displacement during the evaluation. The rationale for passing the EndoFLIP® trans-nasally was that the subjects with total laryngectomy recruited in this study already had a local anaesthetic spray administered to the nares by a member of the ENT team before their EndoFLIP® evaluation and had a different scope passed trans-nasally as part of their routine ENT care.

3.5.1.3. Data Analysis

Distensibility and POS opening during swallowing data from total laryngectomy studies was analysed as previously described for healthy adult studies (refer to Chapter 3.3.3 for UOS distensibility and UOS opening during swallowing data analysis respectively).

3.5.1.4. Statistical Analysis

Data was entered into SPSS statistical software package (version 19j (IBM CORP, New York, U.S.A.). According to Shapiro-Wilks, data was not normally distributed and therefore was expressed as medians (inter-quartile range (IQR)) and non-parametric tests were employed. Kruskal-Wallis tests were used to determine a change in POS CSA and IBP across balloon volumes (1, 5, 10, 15 and 20mls) during distensibility testing and to establish differences in median POS diameter, IBP and duration of POS opening at baseline and across dry, 5ml and 10ml liquid swallow events. Significance was set at $P<.05$. Where significance was found, multiple comparisons were made using the Wilcoxon rank sum test. Bonferroni correction was made and post-hoc tests were significant at an adjusted alpha level of 0.0127.Wilcoxon rank sum tests were employed to; (1) establish median differences in CSA and IBP across laryngectomy and control groups at 1, 5, 10, 15 and 20ml balloon volumes during the 20ml ramp distension and (2) determine median differences in UOS diameter, duration of UOS opening and minimum IBP across groups during dry, 5ml and 10ml liquid swallowing.

3.5.2. Satisfaction of dysphagia clinicians with current UOS evaluation and feedback on the potential role of EndoFLIP® in clinical dysphagia practice

Based on the clinical experience of the researcher, the rationale for this study was that the majority of dysphagia clinicians are not satisfied with current UOS evaluation methods in clinical practice and that this dissatisfaction is evident across therapists with varying levels of experience and from different countries and work settings. To the knowledge of the researcher, challenges in UOS evaluation have not been formally explored to date. Yet, colleagues of varying levels of clinical experience internationally informally report challenges including lack of resources and equipment and access to current UOS evaluations (i.e., VFS, FEES, PM). Based on clinical experience, the researcher purported that data obtained from EndoFLIP® may be deemed useful by clinicians to determine effectiveness of dysphagia interventions and visual imaging of UOS and quantitative data derived from EndoFLIP® would be considered useful in dysphagia evaluation.

A 25-item electronic survey (10-15 minute completion time) was designed by the researcher and piloted with seven SLTs. The survey was refined based on feedback provided. The researcher then posted the survey on an internet-based survey site (www.surveymonkey.com) (see copy of survey in Appendix 6). Emails advertising the survey were sent to 82 SLT managers in the Republic of Ireland (ROI) for dissemination to staff. Of note, SLTs were trained to work with dysphagia at a postgraduate level in ROI up until 2011. Responses from SLTs without active dysphagia caseloads were excluded from the data analysis. Notice of the survey was also forwarded by the researcher to two Dysphagia Special Interest Groups (SIGs) in the United Kingdom (UK) and information pertaining to the survey was included in an edition of Bulletin (Royal College of Speech & Language Therapists (RCSLT). A link to the survey was also posted on the Division 13 American Speech & Hearing Associations' (ASHA) web forum. Descriptive statistics were used to analyse survey finding. Minitab version 14 (250) was

used to determine an association (Pearson's (r) correlation) between satisfaction with current UOS evaluation and level of clinical experience.

3.6. Methodology Summary

Table 3.6 summarises the studies performed by the researcher according to each of the four research questions posed in this thesis. The table outlines the number of subjects recruited for each research study, the associated research setting and the source and timing of ethical approval obtained. It also summarises who inserted the probes during testing and confirms the presence of medical staff during probe insertion as per ethical approval requirements.

In the next chapter, results of each of the studies conducted will be presented.

Table 3.6 Summary of Methodological Design

		Study	Participant Details	Setting	Ethical Approval (see Appendix 4)	Probe Insertion
Research Questions		Reproducibility Study	N/A	Tallaght Hospital, Dublin	N/A	N/A
	1	EndoFLIP® Balloon Insertion and Positioning in UOS under VFS	Two adult males with oro-pharyngeal dysphagia		Approval obtained from St. James' /AMNCH Joint Research Ethics Committee (JREC) in 2009	Researcher inserted probe and Radiology Staff, Tallaght Hospital, were present during probe insertions
		Pilot Studies without VFS guidance	5 healthy adult volunteers recruited over one day period	Neuro-gastro-enterology Clinic, University Hospitals Leuven, Belgium	Approval obtained from St. James' /AMNCH Joint Research Ethics Committee (JREC) in 2009 As these studies were completed in Leuven, ethical approval was also obtained from the Research Ethics Committee, University Hospitals Leuven, Belgium in 2011	Member of Leuven research team (RV/NR) inserted probe and Prof. Jan Tack, Consultant Gastro-enterologist present or Dr. Athanasios Papathan-asopoulos were present during probe insertions
	2	UOS Distensibility	14 healthy adult volunteers recruited over two day period			
		UOS Opening during Swallowing				
		Effect of Postures & Manoeuvres on UOS Opening	Data from 11 of 14 healthy volunteers recruited was included in analysis			
	3	HRM/AIM Analysis- A Comparative Study				
	4	Clinical Studies	10 adults with total laryngect-omy	St. James' Hospital, Dublin	Approval obtained from St. James' /AMNCH Joint Research Ethics Committee (JREC) in 2009	Researcher inserted probe and Member of ENT surgical team present during probe insertions
		Online 25-item survey	224 dysphagia-trained SLTs inter-nationally	Tallaght Hospital, Dublin	N/A	N/A

CHAPTER 4. RESULTS

4.0. INTRODUCTION TO RESULTS

In this chapter, the results of the four key research questions previously described are reported (see Chapter 2.6). Firstly, EndoFLIP® accuracy data is presented. Pilot study findings with and without VFS are described. Next, data on UOS distensibility in fourteen non-elderly (20-50years) healthy subjects using EndoFLIP® is presented. UOS opening patterns during swallowing are also quantitatively measured in this same subject group. The effects of voluntary postures and manoeuvres on UOS opening using EndoFLIP® are reported based on data from eleven of these fourteen subjects. EndoFLIP® measures of UOS opening from eleven of the fourteen healthy subjects were compared to AIM analysis parameters using data from combined HRM-MII. Results from an initial clinical study where EndoFLIP® is employed to evaluate the UOS in a clinical population with known UOS dysfunction are presented. Lastly, results from an online 25-item survey of dysphagia-trained SLTs internationally are provided.

4.1. Research Question 1: Accuracy of EndoFLIP® measures and safe positioning of EndoFLIP® in the UOS in people with dysphagia and in healthy adults

The results of the three sub-questions relating to this first key research question are presented below.

4.1.1. The effect of transducer position within the lumen of the balloon and balloon constriction on accuracy of EndoFLIP® diameter measurements

(i) Transducer Position Test

EndoFLIP® diameter measurement findings based on transducer position tests are depicted in Figures 4.1 to 4.4. For each figure, the diameter measurement profile is depicted at 0° (blue line) and 45° (red line) at 15mmHg and 30mmHg balloon pressures. The SD of measurements at each diameter is included as error bars. The sixteen diameter measurements across each plot were then averaged to obtain the mean value of the cylinder diameter as measured across the profile with the SD also reported.

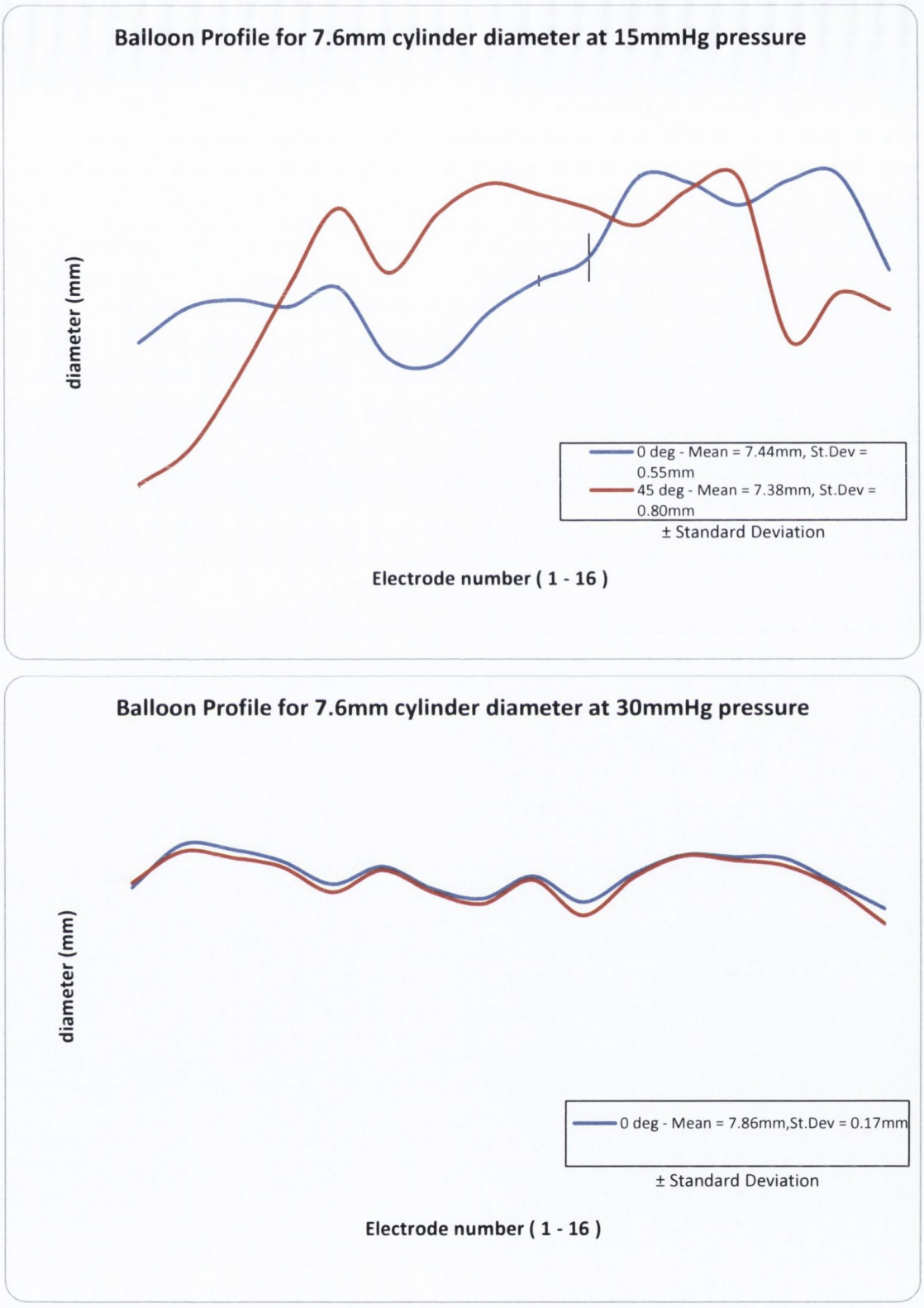

Figure 4.1 Profile of EndoFLIP® probe inside 7.6mm diameter cylinder at a balloon pressure of 15mmHg (top) and 30mmHg (bottom). Probe was held by hand at 0° and 45° angles at the points where it protruded from the cylinder. Values are mean ± standard deviation

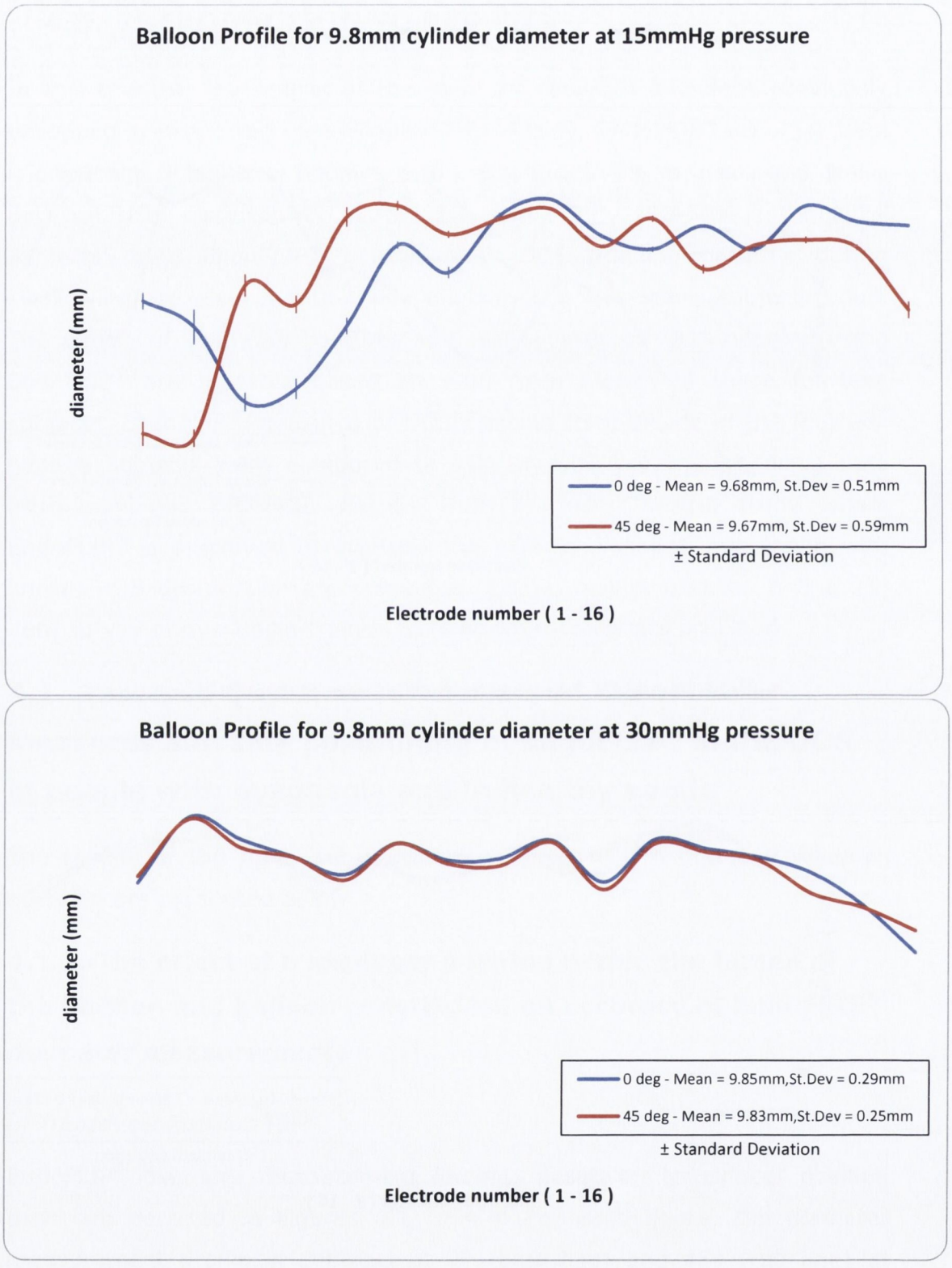

Figure 4.2 Profile of EndoFLIP® probe inside 9.8 mm diameter cylinder at a balloon pressure of 15mmHg (top) and 30mmHg (bottom). Probe was held by hand at 0° and 45° angles at the points where it protruded from the cylinder. Values are mean ± standard deviation

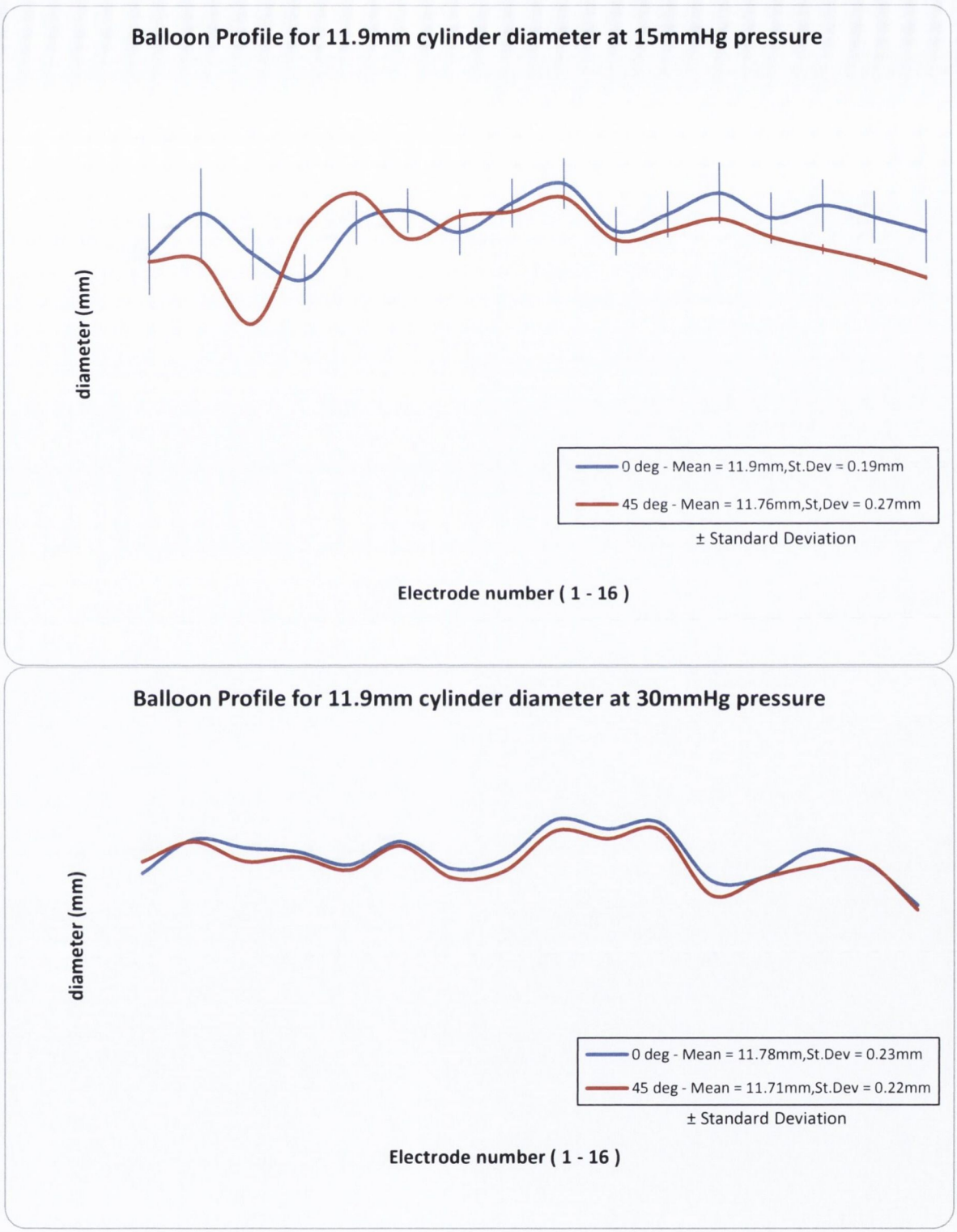

Figure 4.3 Profile of EndoFLIP® probe inside 11.9 mm diameter cylinder at a balloon pressure of 15mmHg (top) and 30mmHg (bottom). Probe was held by hand at 0° and 45° angles at the points where it protruded from the cylinder. Values are mean ± standard deviation

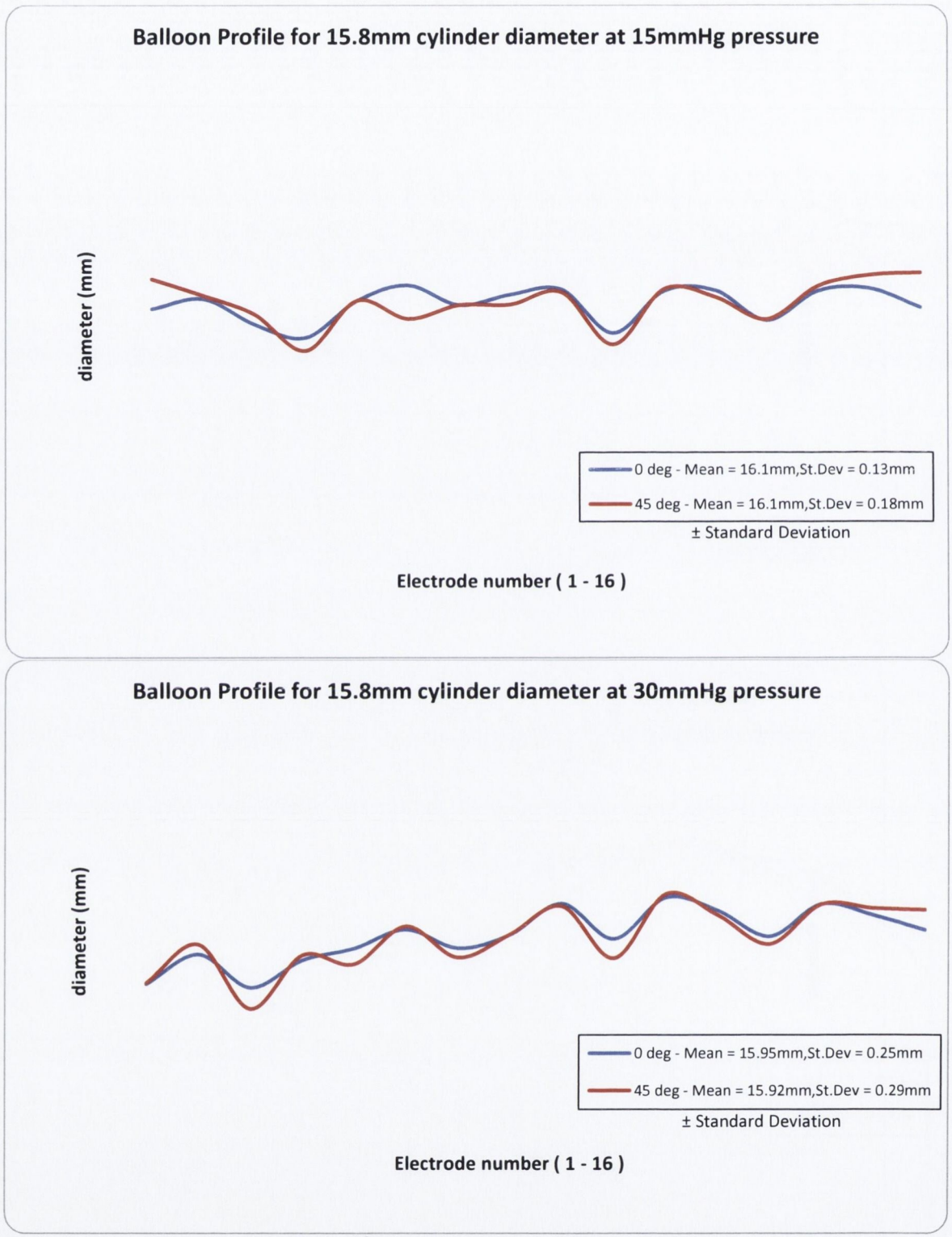

Figure 4.4 Profile of EndoFLIP® probe inside 15.8 mm diameter cylinder at a balloon pressure of 15mmHg (top) and 30mmHg (bottom). Probe was held by hand at 0° and 45° angles at the points where it protruded from the cylinder. Values are mean ± standard deviation

In Table 4.1, the diameter measurement derived from EndoFLIP® can be viewed alongside actual diameter of the cylinder within the diameter measuring block. Percentage differences between measures never exceed 3.4% across both probe angles (0° & 45°) and balloon pressures (15mmHg & 30mmHg). Percentage differences are slightly lower at 30mmHg than 15mmHg and at 0° probe angle compared to 45° probe angle.

Table 4.1 Mean diameter as measured by EndoFLIP® at 15mmHg and 30mmHg for 0° and 45° probe position

	Actual diameter of cylinder (mm)	Mean EndoFLIP® diameter at 0° ±St. Dev (mm)	% difference of measured mean from actual value at 0°	Mean EndoFLIP® diameter at 45° ±St. Dev (mm)	% difference of measured mean from actual value at 45°
15mmHg	7.60	7.44 ± 0.55	- 2.1 %	7.38 ± 0.55	-2.9%
	9.90	9.68 ± 0.51	- 2.2 %	9.67 ± 0.59	-2.3%
	11.90	11.91 ± 0.19	+0.1 %	11.76 ± 0.27	-1.2%
	15.80	16.09 ± 0.13	+ 1.8 %	16.10 ± 0.18	+1.9%
30mmHg	7.60	7.86 ± 0.17	+3.4%	7.82 ± 0.18	+2.9%
	9.90	9.85 ± 0.29	-0.5%	9.83 ± 0.25	-0.7%
	11.90	11.78 ± 0.23	-1%	11.71 ± 0.22	-1.6%
	15.80	15.95 ± 0.25	+1%	15.92 ± 0.29	+0.8%

(ii) Balloon Constriction Test

Findings on the effect of balloon constriction on EndoFLIP® diameter measurements are displayed in Figures 4.5 to Figure 4.8.

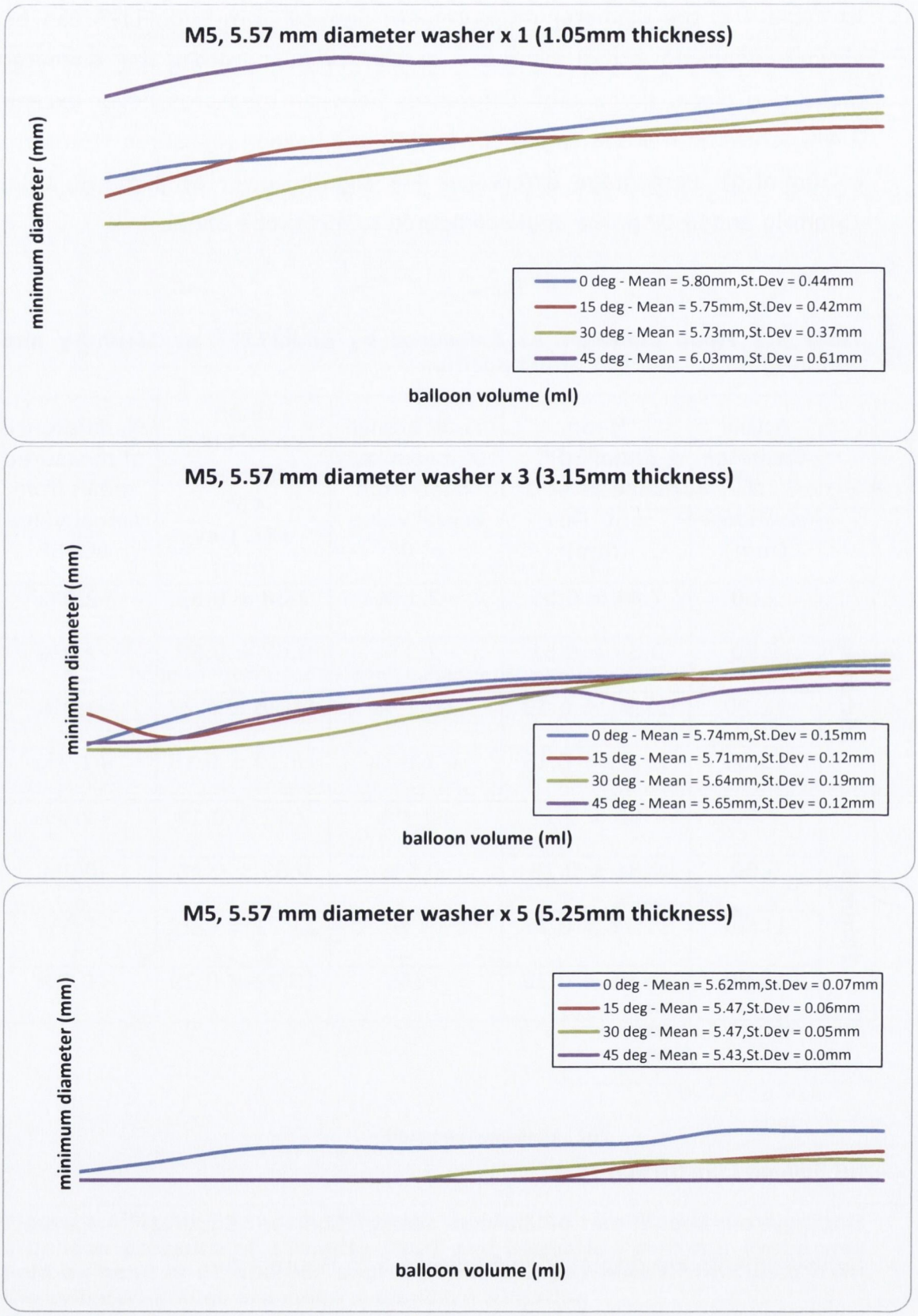

Figure 4.5 Minimum diameter in balloon against balloon volume for a single M5 washer (1.05mm thickness) (top), 3 M5 washers (3.15mm thickness)(middle) and 5 M5 washers (5.25mm thickness) (bottom) for a range of angles

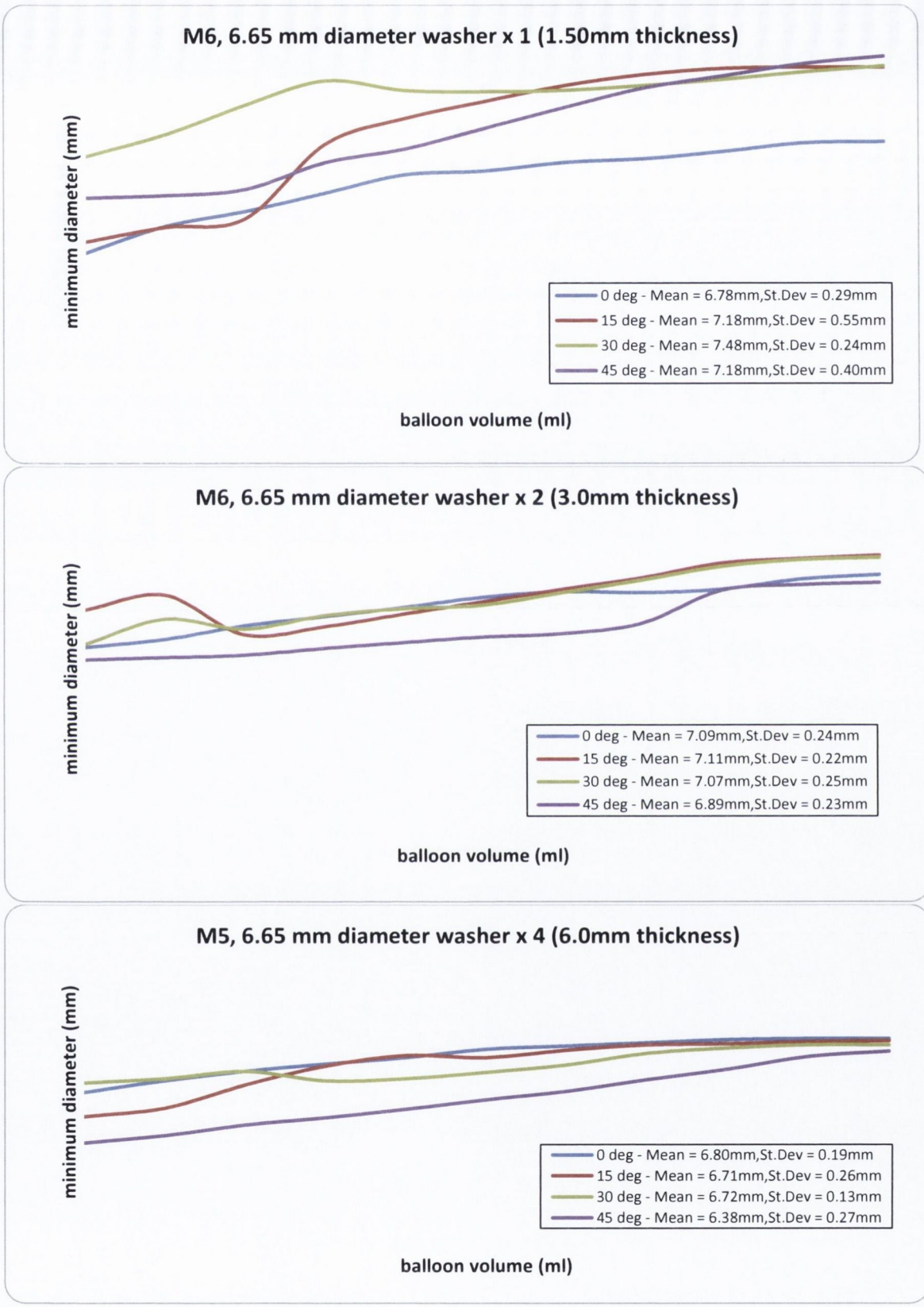

Figure 4.6 Minimum diameter in balloon against balloon volume for a single M6 washer (1.50mm thickness) (top), 2 M6 washers (3.0mm thickness) (middle) and 4 M6 washers (6.0mm thickness) (bottom) constricting the balloon at the midpoint for a range of angles

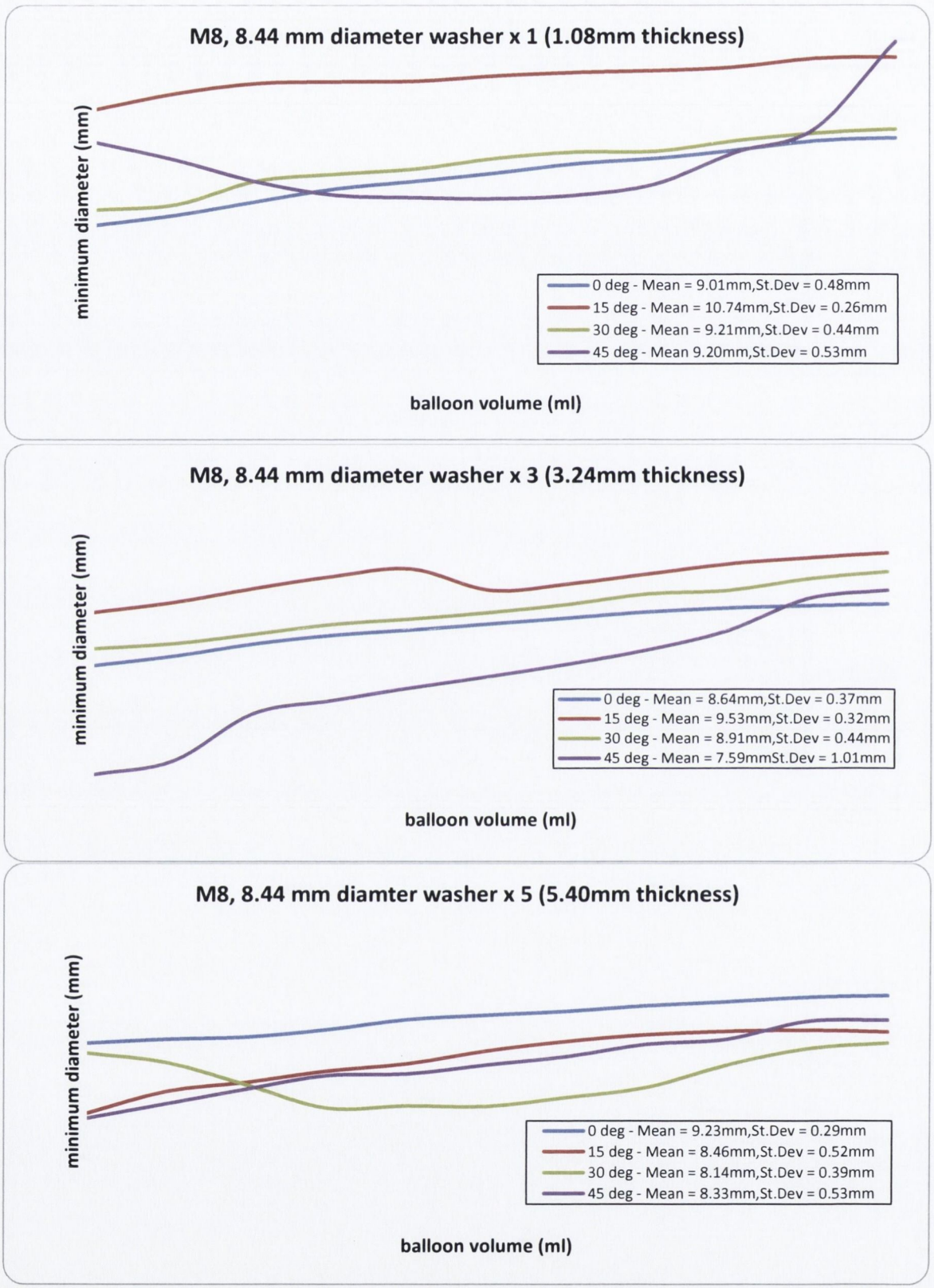

Figure 4.7 Minimum diameter in balloon against balloon volume for 1 M8 washer (1.08mm thickness) (top), 3 M8 washers (3.24mm thickness) (middle) and 3 M8 washers (5.40mm thickness) (bottom) constricting the balloon at the midpoint, of thickness 1.08mm, for a range of angles

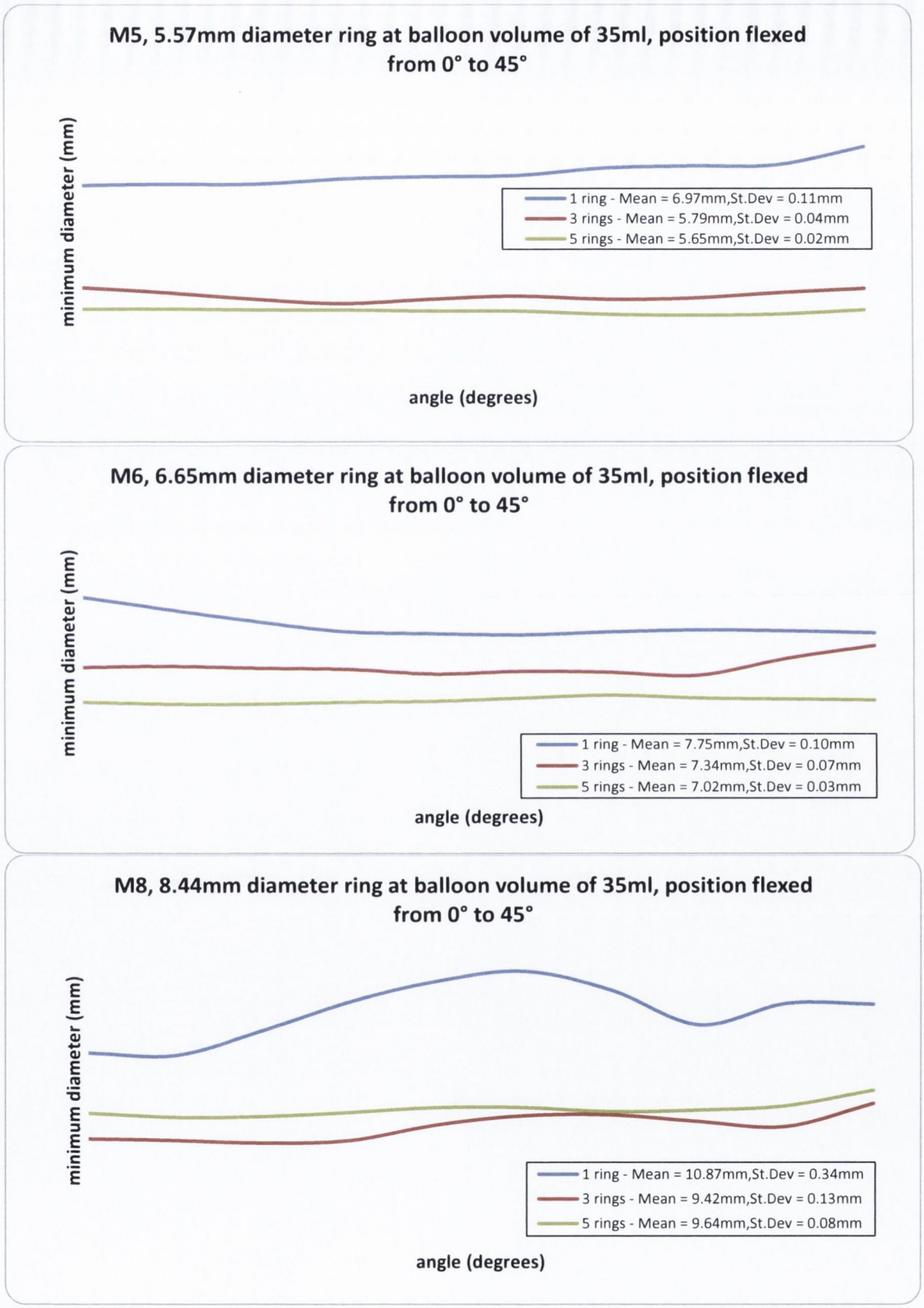

Figure 4.8 Minimum diameter in balloon, held at constant volume of 35ml, as the angle of flexion was changed from 0° to 45°, for different quantities of the M5 (top), M6 (middle) and M8 (bottom) washer

The null hypothesis for accuracy studies was that there would not be adequate accuracy of EndoFLIP® data across varying transducer positions and balloon constrictions during testing. Based on the operational definition of adequate accuracy applied in this study and the findings reported here, this null hypothesis can be rejected. EndoFLIP® data was found to be adequately accurate and the researcher could proceed with further studies. The results of transducer position studies and balloon constriction studies will be discussed in detail in Chapter 5.

Results addressing the safety and positioning of EndoFLIP® under videofluoroscopic guidance in the UOS of people with dysphagia are reported next.

4.1.2. Safe insertion and positioning of EndoFLIP® into the UOS in people with dysphagia

EndoFLIP® was inserted trans-nasally by the researcher (see Audio-Visual Clip 1 in Appendix 7) and the position of the balloon was confirmed fluoroscopically to be in the UOS region during both studies (Figure 4.9). Ramp distensions were completed to 10ml, 20ml, 30ml and 35ml volumes without any airway compromise. During each of these balloon distensions, the narrow region of the UOS was observed on the EndoFLIP® screen (Figure 4.10).

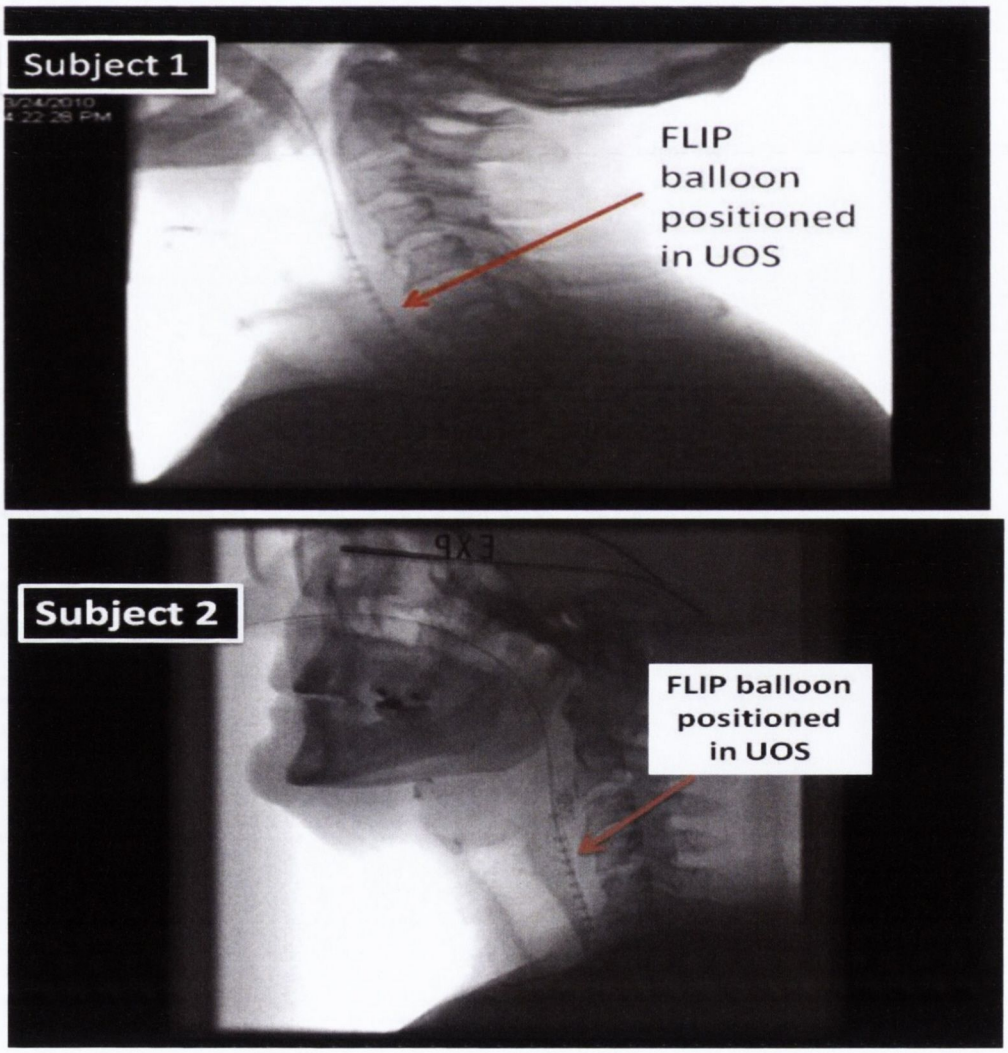

Figure 4.9 EndoFLIP® Balloon safely positioned in the UOS of Two Subjects under VFS

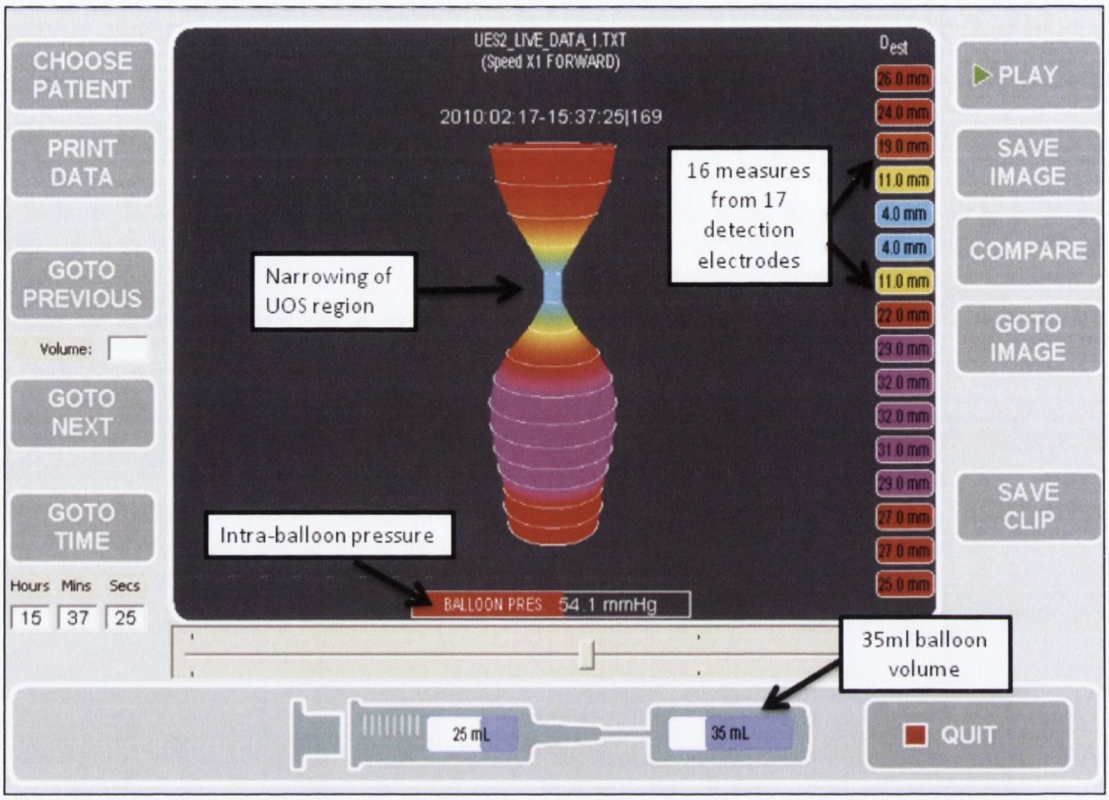

Figure 4.10 Narrowing of UOS Region on EndoFLIP® Screen during Balloon Distensions

When the balloon was filled with 35mls of conductive solution the narrowest UOS diameter was measured at baseline, during dry swallowing and during head turn manoeuvres for both subjects (see Figure 4.11). Preliminary results show the mean narrowest UOS diameter to be 4.15mm at rest (4-4.3mm). This mean increased during dry swallowing to 15.8mm (13.9-17.7mm). Head turn to right increased narrowest UOS diameter from 4.15mm to 5.2mm (4.2-6.4mm). While 35ml balloon volume was well tolerated by subjects, high IBP levels (50-60mmHg) were noted at rest and during swallow events.

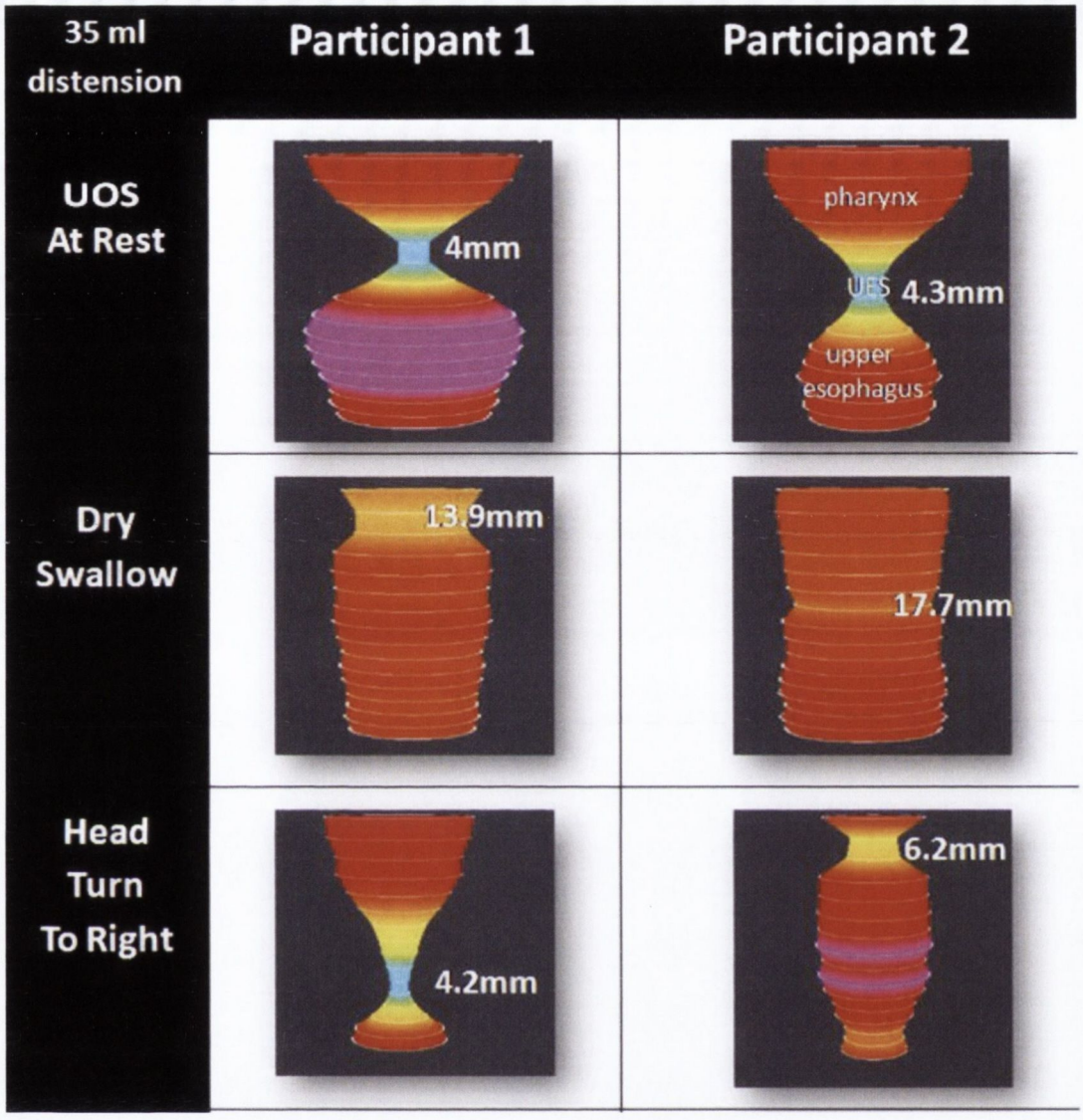

Figure 4.11 Change in Geometric Profile of UOS during Study Protocol

The hypotheses were that (i) EndoFLIP® could be safely inserted into the oesophagus without any serious adverse events; (2) the distended balloon could be positioned in the UOS and distended under videofluoroscopic guidance until the hourglass shape of the UOS could be visualised on the EndoFLIP® screen and (iii) patients with dysphagia would be able to complete voluntary dry swallows and postural manoeuvres with the distended balloon in the UOS. Based on the findings from these studies, these three study hypotheses were accepted. Since it was now evident that EndoFLIP® could be safely positioned in the UOS under VFS guidance, the next question on whether it could be positioned without VFS was addressed.

4.1.3. Safe insertion and positioning of EndoFLIP® into the UOS in healthy adults without videofluoroscopic guidance

The EndoFLIP® probe was passed trans-orally (see Audio-Visual Clip 2 in Appendix 7). Four of five subjects completed the study protocol. Subject 2 did not complete the study due to intolerance of the distended balloon in the UOS for a prolonged period. Subject 1 did not complete voluntary postures and manoeuvres during 5ml liquid swallows as it was only upon completion of this initial study that the researcher ascertained that liquid could be swallowed with the balloon distended in the UOS and then extended the protocol for subsequent studies.

4.1.3.1. UOS Distensibility

Mean increases in IBP and CSA during 20ml ramp distensions are detailed in Table 4.2. During the 20ml ramp distensions, the EndoFLIP® balloon assumed an hourglass shape at the level of the UOS across all subjects (Figure 4.12).

Table 4.2 Change in UOS Cross-Sectional Area and Intra-Balloon Pressure during 20ml Ramp Distension (n=4)

	IBP (mmHg)				*CSA (mm^2)*			
EndoFLIP® Balloon Volume (ml)	**mean**	**SD**	**min**	**max**	**mean**	**SD**	**min**	**max**
5	7.7	7.7	3.7	10.2	20.9	1.9	18.5	23.5
10	13.6	8.7	6.1	22.1	22.1	2.2	19.1	25.5
15	28.63	7.9	17.9	44	23	2.8	19.7	28.4
20	57.4	10.2	46.3	70.3	23.5	2.8	20.2	28.4

Figure 4.12 Geometric Profile of the UOS during Distensibility Testing (20ml balloon volume)

4.1.3.2. UOS Opening during Swallowing

Table 4.3 summarises mean UOS diameter and IBP changes during various dry and 5ml liquid swallows events. Figures 4.13 and 4.14 demonstrate changes in UOS diameter (mm) and IBP (mmHg) during dry swallows and 5ml liquid swallows. Prolonged UOS opening time in two cases (subject 3 & 4) may represent a struggling behaviour in initiating a pharyngeal swallow with a balloon filled with 15mls in the UOS region.

Table 4.3 UOS Diameter and IBP Changes during Swallowing (n=4)

	Manoeuvre	***N***	***Mean Minimum UOS Diameter (mm)***	***Mean Minimum IBP (mmHg)***
	At Rest	4	4.9mm (4.8-4.9, SD: 0.1)	47.2mmHg (35.3-62.9, SD: 11.7)
	Dry Swallow	4	8.9mm (5.2-11.6, SD: 2.9)	9.9mmHg (4.4-20.7, SD: 7.4)
5ml Liquid Swallows	**Baseline**	4	8.1mm (5.3-10.5, SD: 2.3)	9.7mmHg (8-16.7, SD: 5.2)
	Head Turn Right	3	10.1mm (5.1-15.8, SD: 5.4)	2.5mmHg (-2.3-5.4, SD: 4.2)
	Head Turn Left	3	9.4mm (5.1-15.9, SD: 5.7)	4mmHg (-0.3-7.2, SD: 3.8)
	Chin Tuck	3	8.9mm (4.9-12.7, SD: 3.9)	7.4mmHg (4.2-10.76, SD: 3.3)
	Effortful Swallow	3	9.3mm (4.9 - 15.2, SD: 5.3)	0.9mmHg (- 4.7-10.8, SD: 8.7)
	Mendelsohn Manoeuvre	3	9.6mm (5.0- 14.7, SD:4.9)	7.2mmHg (2.7-10.2, SD: 4)
	Supraglottic Swallow	3	9.2mm (5-15.2, SD: 5.4)	3.4mmHg (-0.6-5.4, SD: 3.4)

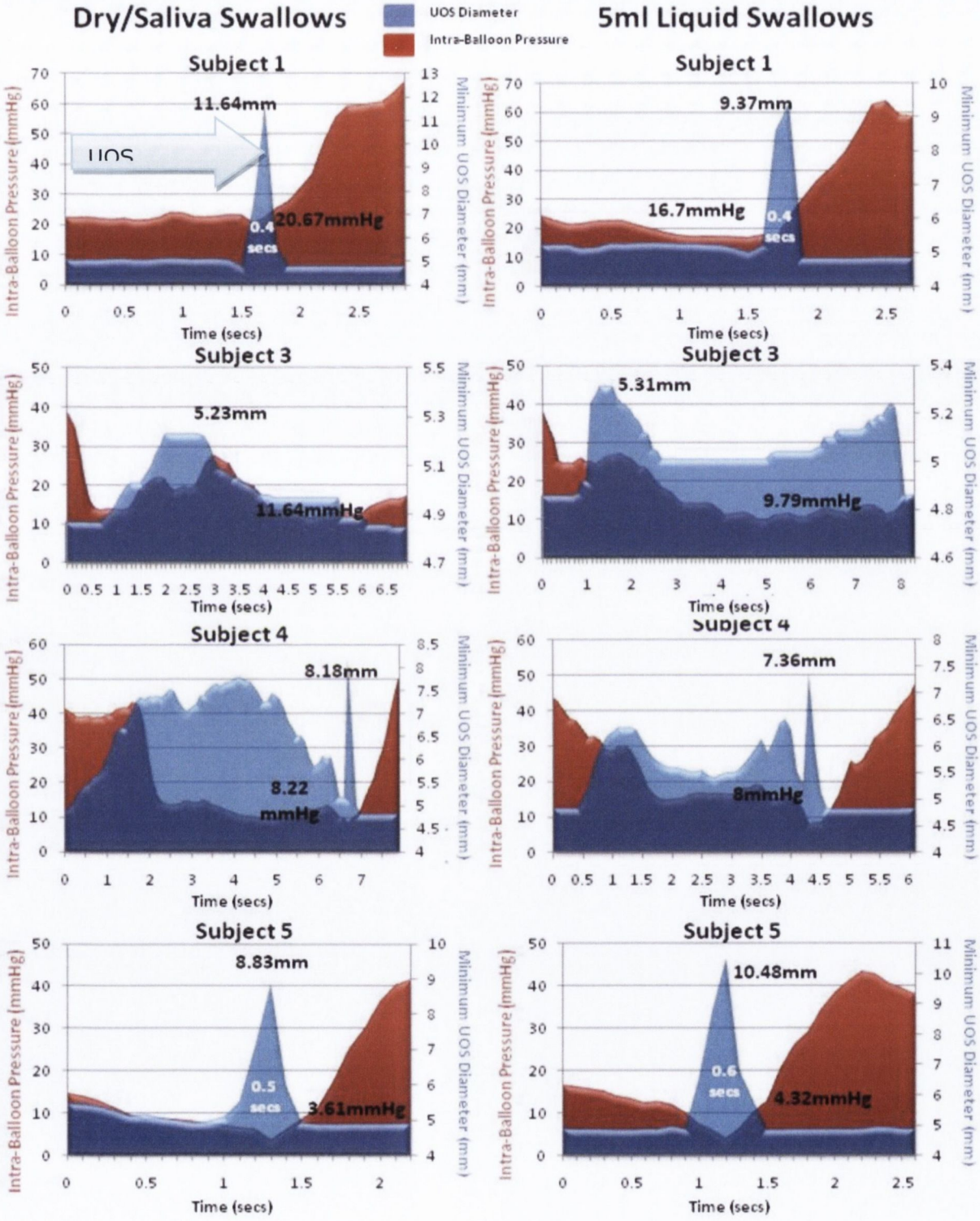

Figure 4.13 UOS Diameter and IBP Changes during Swallowing (n=4)

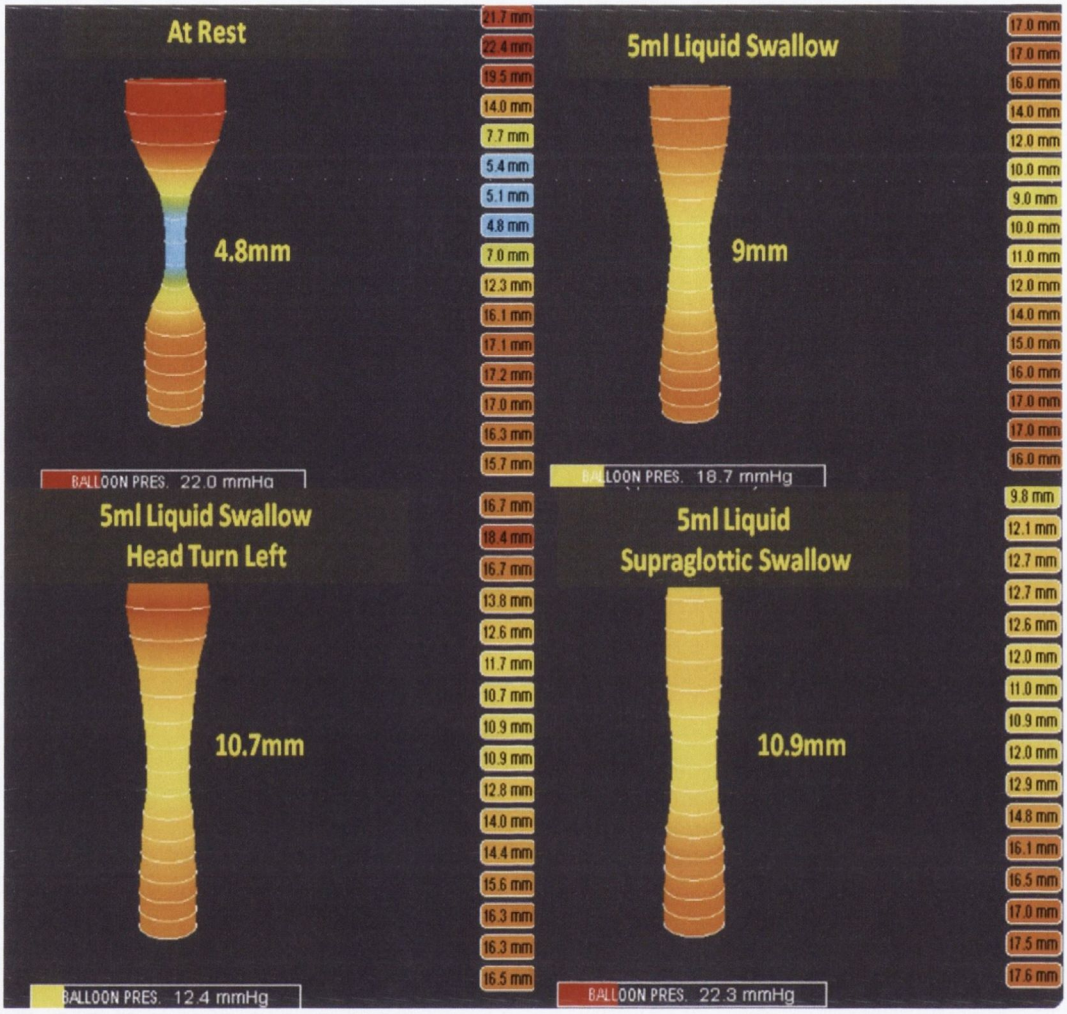

Figure 4.14 Geometric Profile of the UOS during Postural Strategies in One Subject

The researcher had hypothesised that (i) EndoFLIP® could be safely and accurately inserted and positioned in the UOS without VFS guidance and that (ii) subjects would be able to perform swallows and postural manoeuvres commonly employed in clinical practice with the distended EndoFLIP® balloon in position in the UOS and (iii) preliminary temporal, diameter and IBP data relating to the UOS could be acquired. Each of these three hypotheses can be accepted based on the findings presented here.

The second key research question relating to the ability of EndoFLIP® to acquire normative data on UOS distensibility and UOS opening during swallowing is considered next.

4.2. Research Question 2: Normative data on UOS distensibility and UOS opening during swallowing in an adult healthy group using EndoFLIP®

To address the second key research question, four sub-questions were addressed. The results associated with these four questions are described below.

4.2.1. UOS distensibility in an adult healthy group using EndoFLIP®

The EndoFLIP® probe was safely inserted and the narrowing of the UOS was identified on the EndoFLIP® screen across all fourteen subjects. Thirteen of fourteen subjects completed 20ml ramp distensions (see individual distensibility graphs in Appendix 8). One subject (subject 11) was unable to tolerate more than 16mls in the inflated balloon in the UOS for prolonged periods. The data from this subject was therefore omitted from distensibility data analysis. The second of two 20ml ramp distensions was included in data analysis to allow for an accommodation effect. One subject (subject 13) did not reach a maximum of 20ml balloon volume on their second distension (18mls) and hence their first distension (20mls) was selected for data analysis.

Across all subjects, the hourglass shape of the UOS could be visualised on the EndoFLIP® screen during the ramp distension. Geometric profiles of the UOS on the EndoFLIP® screen across subjects at 20ml balloon volume are shown in Figure 4.15.

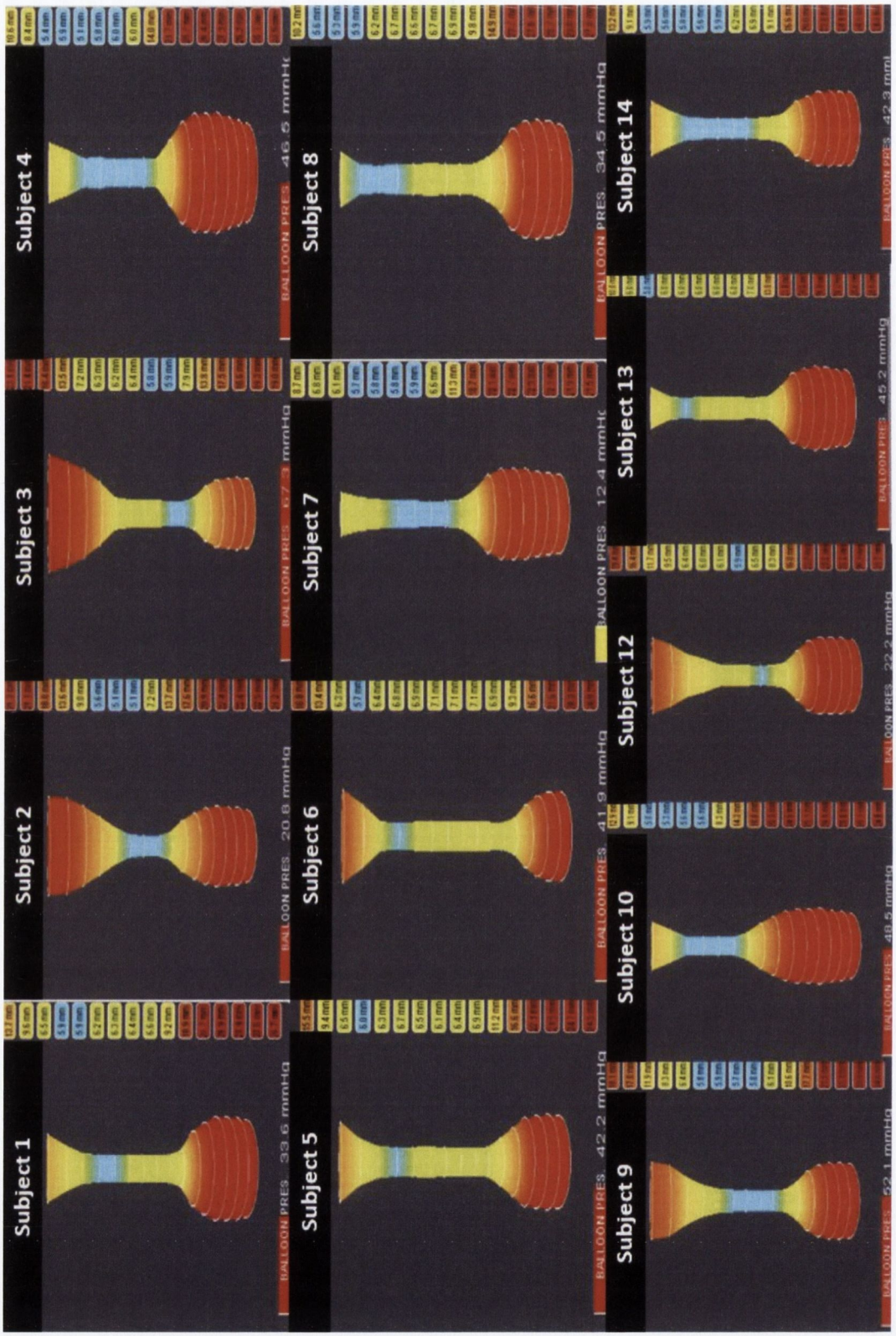

Figure 4.15 Geometric Profile of the UOS on EndoFLIP® Screen at 20ml Balloon Volume across Subjects (n=13)

The minimum UOS CSA increased significantly during the 20ml ramp distension as the balloon volume increased ($H(2)=18.32$, 4 d.f., $p<.001$) (Figure 4.16). An increase approaching statistical significance in median UOS CSA was found between 1m and 5ml balloon volumes (median CSA 18.7 mm^2 and 22.5mm^2 respectively) ($p=0.028$- not significant due to adjusted alpha level of 0.01) and there was a statistically significant increase in UOS CSA between 5 and 10 ml balloon volumes (median CSA 22.5mm^2 and 23.8mm^2 respectively) ($p<.001$). The UOS then resisted any further increase in CSA during the distension, as no statistically significant difference in median CSA was observed between 10mls and 15mls ($p=0.382$) or between 15mls and 20mls ($p=0.382$) (Figure 4.17).

IBP also increased significantly during the 20ml ramp distension ($H(2)=27.36$, 4 D.F., $p<.001$) (Figure 4.16). No statistically significant difference in median IBP was found between 1 and 5mls ($p=0.463$) or between 5 and 10 mls ($p<.861$). However, once balloon inflation caused the UOS CSA to reached a plateau, a statistically significant increase in IBP was detected between 10mls and 15mls (4 and 13.4mmHg respectively) ($p=0.004$) and between 15ml and 20mls (13.4 and 36.9mmHg respectively) ($p=0.003$) (Figure 4.17).

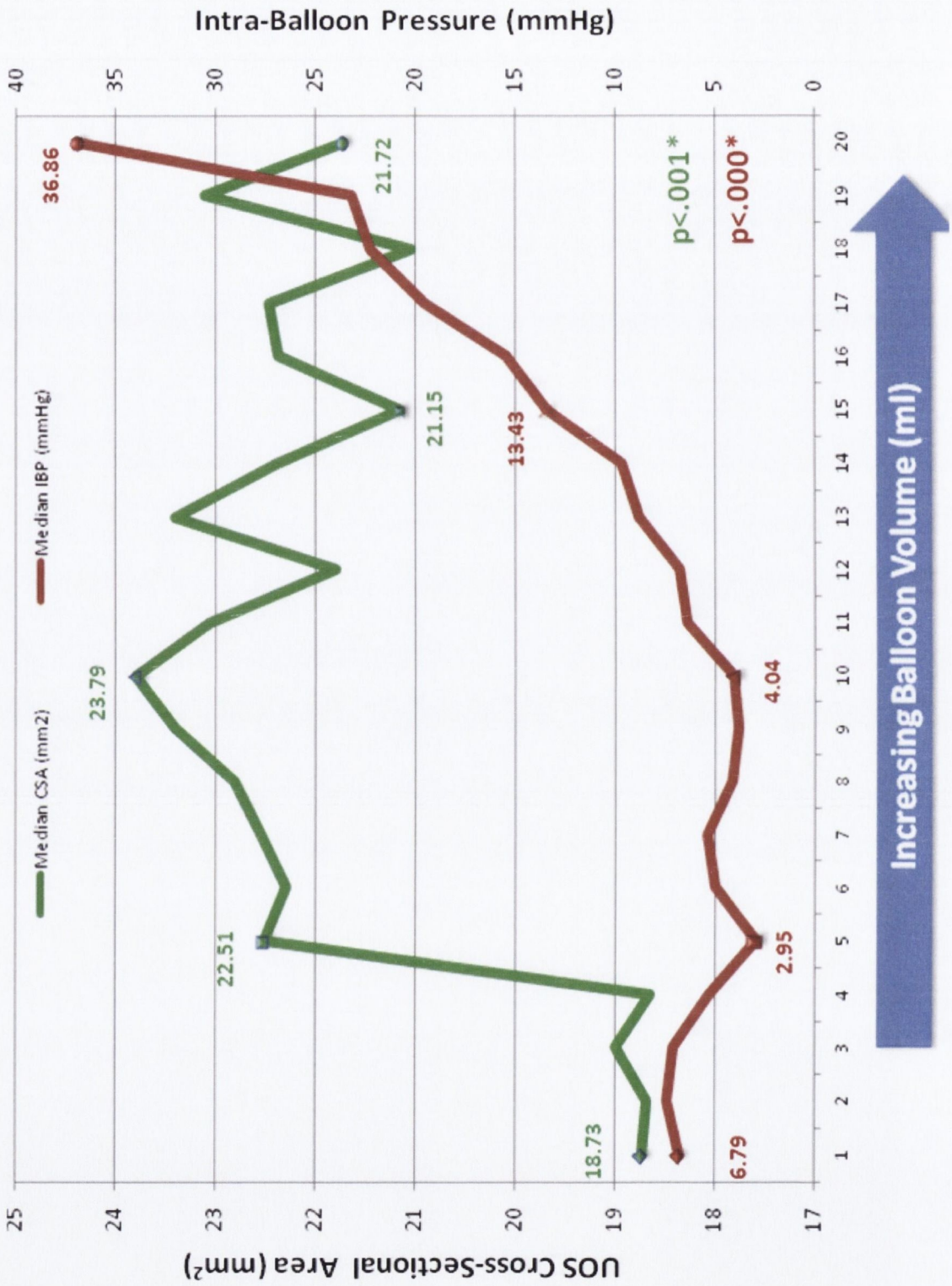

Figure 4.16 Change in UOS CSA and IBP during 20ml Ramp Distension (n=13)

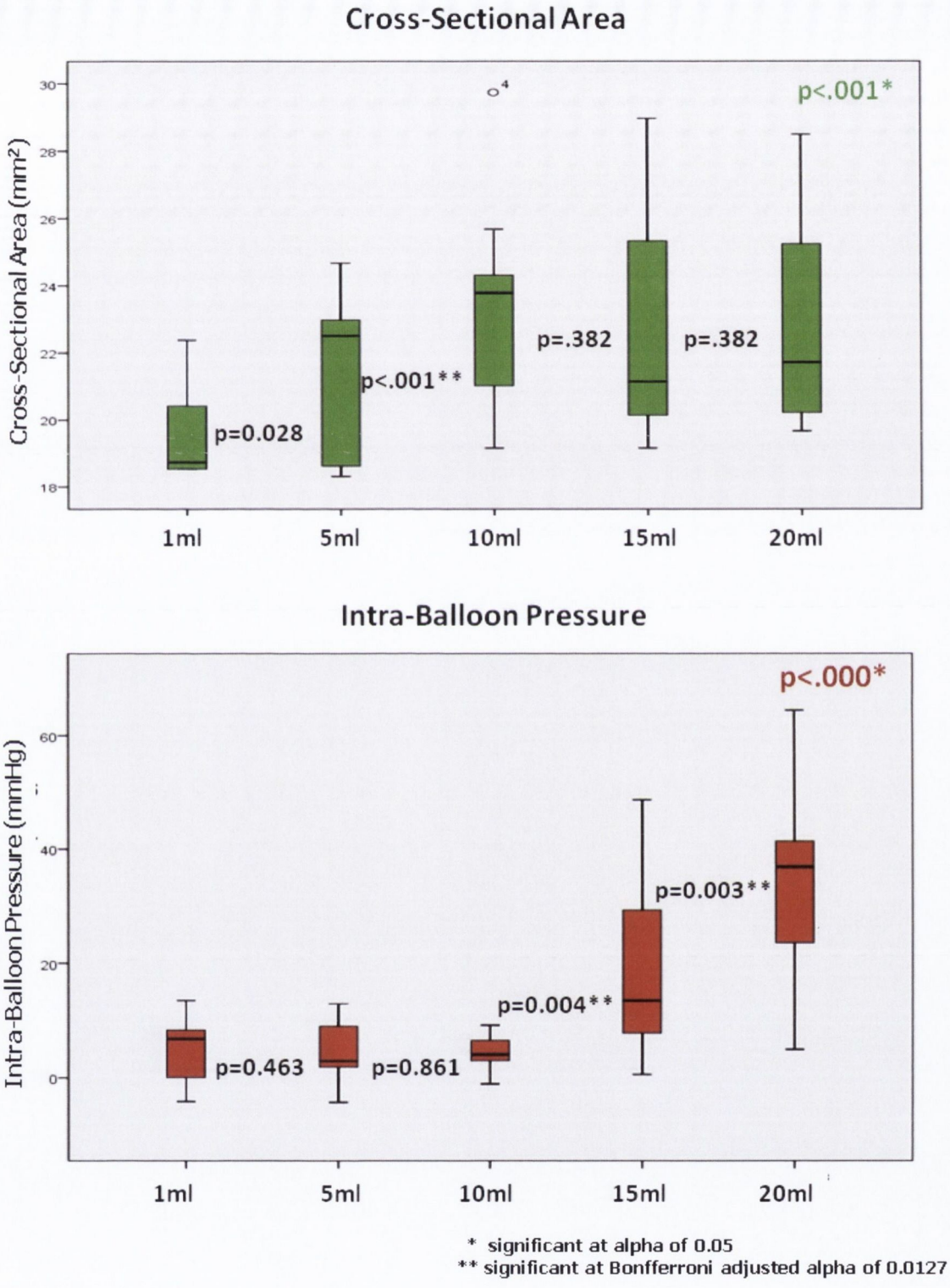

Figure 4.17 UOS CSA and IBP Measures during 20ml Ramp Distension

The hypotheses for this study were that UOS CSA would stop increasing significantly during distensibility testing due to adequate UOS tone in this healthy subject group and IBP would increase significantly during balloon distension. Based on statistically significant findings reported here, both of these hypotheses can be accepted.

Next, results addressing EndoFLIP® measurement of UOS opening during swallowing across bolus volumes are presented.

4.2.2. UOS opening during swallowing in an adult healthy group using EndoFLIP® and creation of colour contour plots of swallowing

Thirteen of fourteen subjects completed the entire swallow events protocol with the distended EndoFLIP® balloon (12mls) within the UOS. To view the geometric profile of the UOS on the EndoFLIP® screen during this study protocol, see Audio-Visual Clip 3 in Appendix 7. One subject (subject 12) could not tolerate the distended balloon in the UOS for the entire protocol and was omitted from swallow manoeuvres data analysis.

Data at rest and from thirty-nine swallows (the second dry, 5ml & 10ml liquid swallows) within the subject group was analysed to obtain group measures of UOS diameter, IBP & duration of UOS opening across swallow events (Table 4.4). There was a statistically significant change in UOS diameter across swallow events ($p<.001$). During dry swallowing, UOS diameter increased significantly from a baseline diameter measure of 4.9mm to 9.6mm (IQR 1.3) ($n=13$) ($p<.001$). Resting median UOS diameter also increased significantly from 4.9mm to 8.61mm (IQR 2.7) during 5 liquid swallows ($p<.001$). Diameter increased from 4.9mm at baseline to 8.27mm (IQR 1.6) during 10ml liquid swallows ($p<.001$). A significant median difference was also observed in UOS diameter between dry and 10ml liquid swallows ($p<.005$). However, no statistically significant difference in UOS diameter was observed during dry and 5ml swallows ($p=0.64$) or between 5ml and 10ml liquid swallows ($p=0.46$) (Figure 4.18).

No statistically significant difference was evident in duration of UOS opening across swallow events ($n=13$) ($p=0.91$) (Figure 4.18). Median duration of UOS opening remained at 0.5 seconds across subjects during dry swallowing (IQR 0.3), 5ml liquid swallows (IQR 0.3) and 10ml liquid swallowing (IQR 0.1) (Figure 4.18).

Table 4.4 EndoFLIP® Measures of Swallowing across Bolus Volumes (n=13)

	Minimum UOS Diameter (mm)				Minimum Intra-Balloon Pressure (mmHg)				UOS Opening Duration (secs)		
No.	**base**	**dry**	**5ml liquid**	**10ml liquid**	**base**	**dry**	**5ml liquid**	**10ml liquid**	**dry**	**5ml liquid**	**10ml liquid**
1	4.88	10.26	7.2	8.27	18.69	6.55	6.64	2.96	0.7	0.5	0.5
2	4.9	9.7	7.9	8.53	14.97	20.19	12.14	10.4	0.4	0.6	0.5
3	4.86	9.46	8.61	7.91	18.54	1.62	4.46	2.82	0.3	0.6	0.5
4	4.89	9.63	8.62	8.92	26.24	1.71	8.12	9.17	0.6	0.3	0.5
5	4.96	8.8	8.75	7.62	19.31	5.08	7.17	7.06	0.3	0.3	0.4
6	4.9	8.87	9.95	9.02	18.85	3.6	7.07	6.66	0.5	0.4	0.2
7	4.87	9.53	6.25	10.02	18.84	-0.02	-1.4	0.35	0.4	0.5	0.5
8	4.87	9.55	10.15	7.95	18.62	2.1	3.36	2.64	0.4	0.3	0.5
9	4.94	7.58	7.3	7.06	19.16	7.48	4.75	1.84	0.3	0.6	0.6
10	4.89	10.84	10.48	6.05	19.58	4.68	4.32	5.78	0.7	0.6	0.5
11	4.9	9.99	8.12	9	31.01	-1.93	-0.23	-2.99	0.7	0.7	0.5
13	4.88	10.93	6.5	6.89	14.82	2.78	7.09	5.64	0.5	0.5	0.4
14	4.88	8.49	9.85	8.41	15.07	4.29	-3.73	2.8	0.6	0.6	0.7

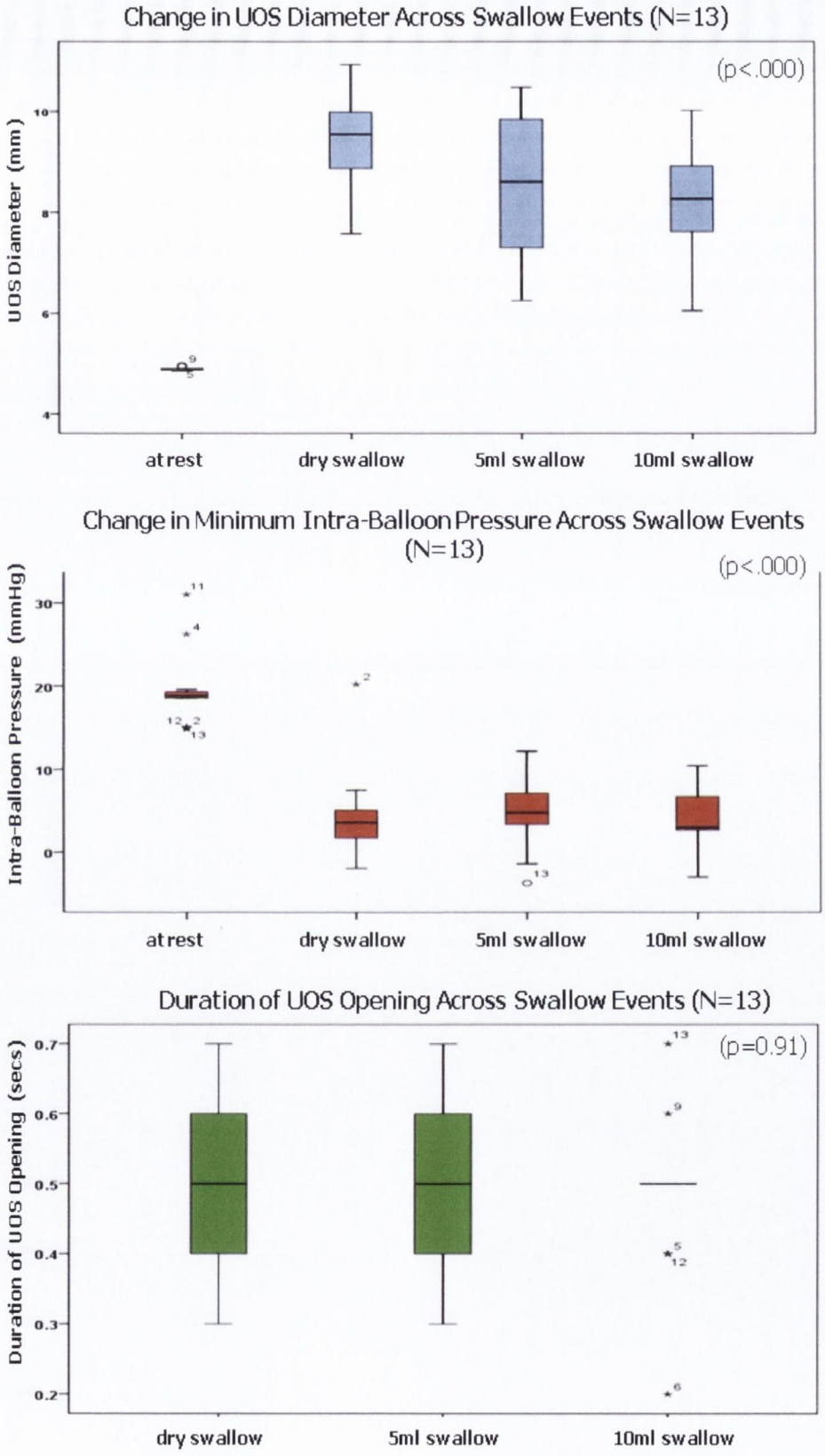

Figure 4.18 Change in UOS Opening Measures during Swallowing across Bolus Volumes

A statistically significant difference in minimum IBP was observed across swallow events ($p<.001$). Resting IBP dropped from 18.8 to 3.6mmHg (IQR 4.1) during dry swallowing ($p=0.002$). IBP dropped from 18.8mmHg at baseline to 4.8mmHg (IQR 5.5) during 5ml swallows ($p<0.001$) (Figure 4.18). Pressure dropped from 18.8 to 2.96mmHg (4.6) during 10ml liquid swallows ($p<0.001$). There was no statistically significant difference in IBP between dry and five ($p=0.6$) or ten ml ($p=0.86$) swallows or between five and ten ml swallows ($p=0.35$) (Figure 4.18).

Once plots within Miscrosoft Excel were examined (Figure 4.19), colour contour plots were produced using Origin Pro software (Figure 4.20 & 4.21) In these plots, time is on the x-axis and sixteen diameter measurements from seventeen detection electrodes spaced 5mm apart within the within the EndoFLIP® balloon are displayed on the y-axis. Each diameter measure is assigned a colour (see legend). The narrowest diameter measures (in red) are at the level of the UOS.

Figure 4.20 depicts the narrow band of UOS (median diameter 4.9; IQR 0.02) at rest over time. At rest, the median length of the UOS was 3cm (IQR 1.7; mean 3.3cm) across subjects (Figure 4.20i). This is in keeping with manometric measurements of UOS length (see Chapter 2.2.1). As the EndoFLIP® balloon is 10cm long, an increased diameter is visible above and below the UOS region, representing the pharynx and upper oesophagus respectively. The black line represents IBP over time. Median resting IBP is 18.8mmHg (IQR 2.7) over time across subjects.

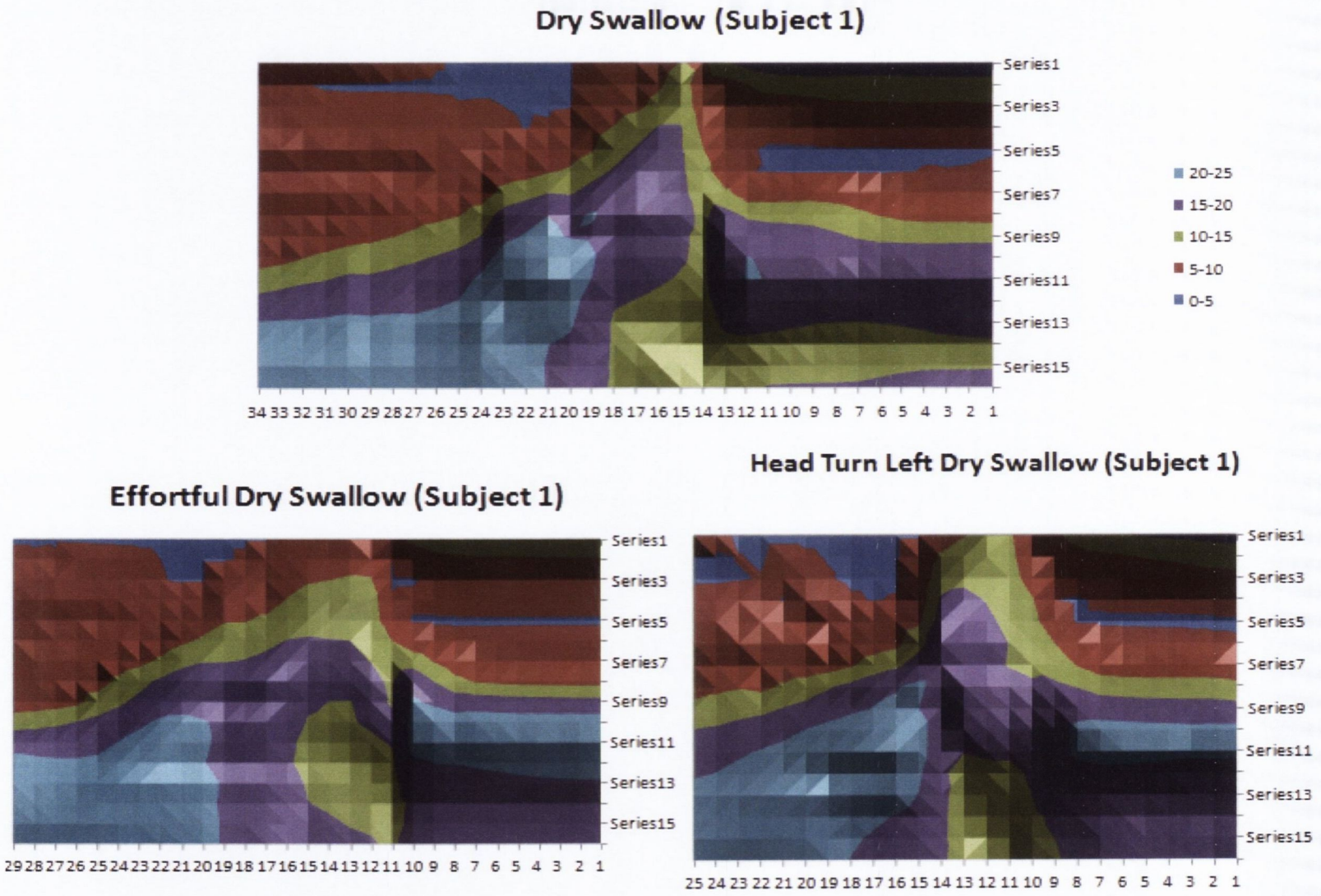

Figure 4.19 Colour Contour Plots of EndoFLIP® Data during a Dry Swallow

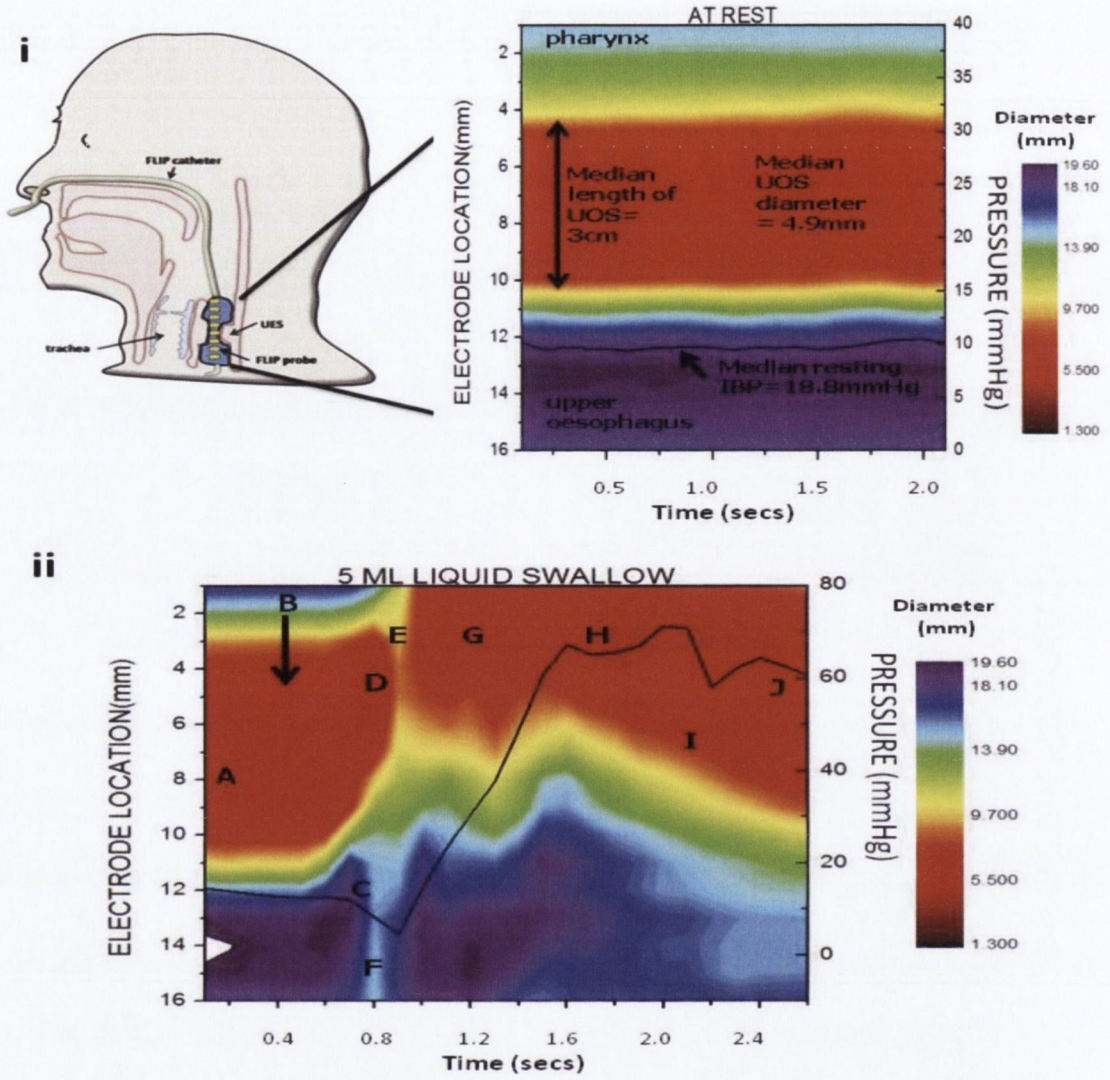

Figure 4.20 Colour Contour Plots of EndoFLIP® Data (i) at rest and (ii) during Swallowing[18]

In Figure 4.14ii, (A) resting UOS diameter is 4.9mm and the resting UOS length is 4cm. As (B) the swallow is elicited, (C) a drop in IBP from its baseline shortly precedes (D) a 2cm upward shift of the UOS, presumably caused by hyo-laryngeal excursion due to suprahyoid muscle contraction. Due to the 5mm spacing between electrodes, the extent of this upward shift during swallowing can be quantified on the colour contour plot. (E) The UOS lumen then opens to 9mm during swallowing. At the point of UOS opening, IBP reaches its minimum point. (F) A narrowing within the upper oesophagus is evident at the point of UOS opening, perhaps due to peristalsis as the bolus enters the oesophagus. (G) The UOS then closes and (H) IBP increases markedly. (I) The UOS returns to its resting position and (J) IBP gradually decreases.

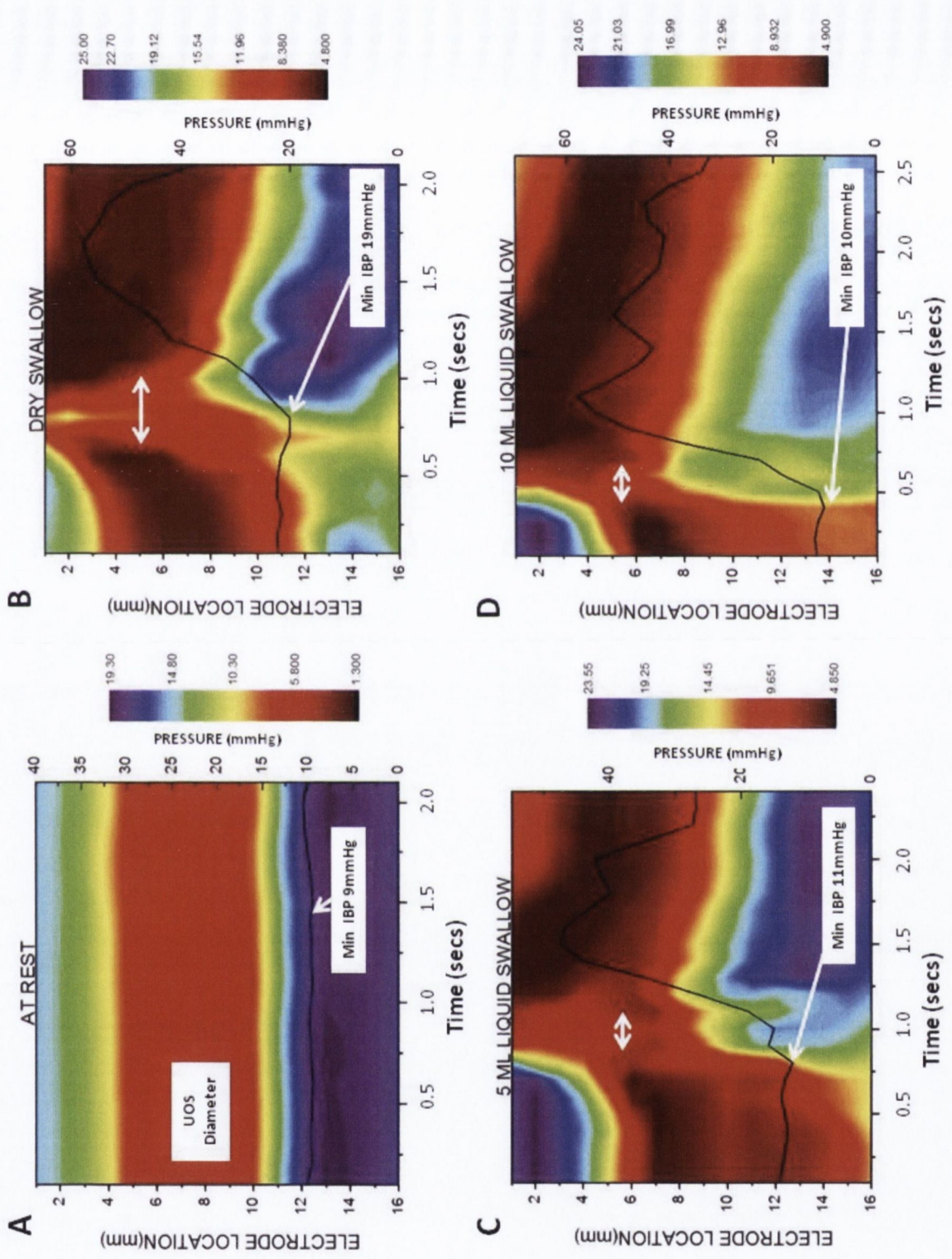

Figure 4.21 Colour Contour Plots of the UOS at Rest and during Dry, 5ml and 10ml Liquid Swallows

The sequence of diameter and pressure changes over time during swallowing is represented in the colour contour plots (Figure 4.20 & 4.21). Initially, IBP drops from its baseline. This pressure drop is followed by a 2cm upward shift of the UOS, presumably caused by hyo-laryngeal excursion upon suprahyoid muscle contraction. Plots allow the position of diameter changes to be evaluated due to the 5mm spacing between electrodes within the EndoFLIP® balloon. The UOS lumen subsequently opens, the extent and duration of which can be measured on contour plots. At the point of UOS opening, IBP reaches its minimum point. A narrowing is also evident at the time of swallowing in the upper oesophagus, which may be indicative of oesophageal peristalsis. When the UOS closes, it returns back to its resting position and IBP increases markedly (Figure 4.20). These observations are evident in a common sequence across dry, 5ml and 10ml liquid swallows (Figure 4.21).

The alternative hypotheses for this sub-question were that (i) UOS diameter would increase significantly from baseline during dry and liquid swallowing; (ii) duration of UOS opening could be captured during swallow events; (iii) IBP would decrease significantly from baseline during dry and liquid swallowing and (iv) an increase in extent and duration of UOS opening and in drop in IBP would be observed with increasing bolus volumes. The researcher also hypothesised that EndoFLIP® data could be used to create colour contour plots of swallowing measures. The findings in this study indicate that all hypotheses can be accepted except for hypothesis (iv). As UOS diameter, duration of UOS opening and minimum IBP did not increase with increasing bolus volume, this hypothesis must be rejected. These findings will be discussed in more detail in Chapter 5.

Results addressing gender differences in UOS distensibility and UOS opening during swallowing as measured by EndoFLIP® are presented next.

4.2.3. Gender differences in EndoFLIP® measures of UOS distensibility and UOS opening during swallowing in an adult healthy group

UOS Distensibility

A statistically significant difference in UOS CSA was detected across genders at both 1ml and 5ml balloon volumes ($p=0.004$ and 0.005 respectively). UOS CSA was slightly higher in females at both of these balloon volumes, which may suggest that UOS tone was slightly lower in females. There was no significant difference in UOS CSA between genders at 10, 15 and 20ml balloon volumes (Figure 4.22 & Table 4.5).

There was a statistically significant difference in IBP across genders at 1, 5, 10 and 15ml balloon volumes. Males presented with significantly higher IBP at 5, 10ml and 15ml balloon volumes. In both males and females, IBP raised markedly between 10 and 15ml balloon volume. In both genders, pressure reached between 30-35mmHg at the end of the 20ml ramp distension (Figure 4.22).

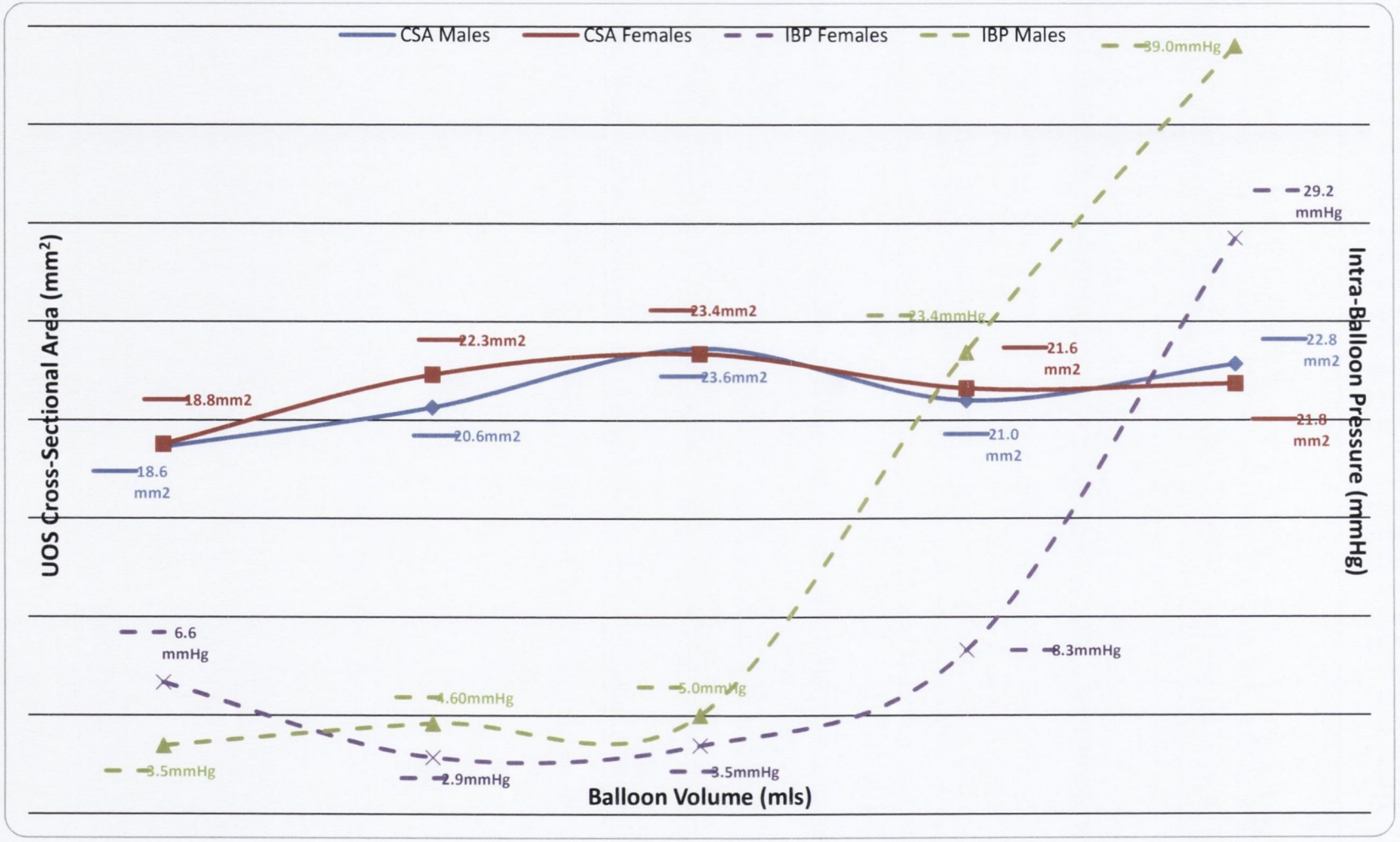

Figure 4.22 Change in UOS CSA and IBP during 20ml Ramp Distension in Males (n=6) and Females (n=7)

Table 4.5 Differences in UOS CSA and IBP across Genders during Distensibility Testing

	Median CSA (mm^2)				Median IBP (mmHg)			
Balloon volume (mls)	**Males (n=6)**	**Females (n=7)**	**Z score**	**P value**	**Males (n=6)**	**Females (n=7)**	**Z score**	**P value**
1	18.62	18.77	-2.87	**.004***	3.46	6.64	-2.80	**.005***
5	20.63	22.30	-2.80	**.005***	4.59	2.86	-2.395	**.017***
10	23.64	23.36	-1.07	.285	5.00	3.47	-2.701	**.007***
15	20.99	21.60	-1.17	.241	23.43	8.29	-2.80	**.005***
20	22.84	21.84	-.255	.799	39.02	29.23	-1.274	.203

These results are discussed in detail in Chapter 5. As gender differences in UOS distensibility have now been established, differences in UOS opening during swallowing across genders are considered next.

UOS Opening During Swallowing

UOS diameter was significantly wider in females at baseline (p=0.034). UOS diameter was also increased in females during dry swallowing (p=0.043). There was no difference in UOS diameter across genders during 5ml and 10ml liquid swallows (p=0.686 & p=0.686 respectively) (Table 4.6). No difference was observed in duration of UOS opening between genders at rest or during dry, 5ml or 10ml liquid swallows (Table 4.6).

Table 4.6 Differences in EndoFLIP® Measures of Swallowing across Genders

EndoFLIP® Measure	Bolus Vol	Male (n=5) Median (IQR)	Female (n=8) Median (IQR)	Z value	P value
UOS Diameter (mm)	Baseline	4.87 (0.05)	4.90 (0.02)	-2.121	**0.034***
	Dry	9.46 (1.5)	9.85 (1.64)	-2.023	**0.043***
	5ml Liquid	8.61 (3.23)	8.37 (2.28)	-.405	0.686
	10ml Liquid	7.95 (1.73)	7.95 (1.91)	-.405	0.686
UOS Opening Duration (secs)	Dry	0.4 (0.2)	0.55 (0.28)	-1.069	0.285
	5ml Liquid	0.6 (0.2)	0.5 (0.28)	-1.289	0.197
	10ml Liquid	0.5 (0.15)	0.5 (0.1)	-1.342	0.180
Minimum Intra-Balloon Pressure (IBP)	Baseline	18.62 (2.19)	19.08 (8.68)	-.948	0.343
	Dry	2.10 (5.09)	4.14 (4.21)	-.405	0.686
	5ml Liquid	3.36 (2.04)	7.08 (2.98)	-2.023	**0.043***
	10ml Liquid	2.64 (1.72)	6.22 (5.01)	-2.023	**0.043***

IBP did not differ between males and females at rest ($p=0.343$). Minimum drop in IBP during swallow also did not vary significantly between males and females ($p=0.686$). However, a statistically significant difference in minimum IBP was observed during 5ml ($p=0.043$) and 10ml ($p=0.043$) liquid swallowing. At both 5ml and 10ml bolus volumes, minimum IBP dropped to a lower minimum in male subjects (Table 4.6).

The alternative hypotheses for this study were that (i) statistically significant differences in CSA and IBP would be observed across 1, 5, 10, 15 and 20ml balloon volumes during ramp distensions and (ii) statistically significant differences in UOS diameter, duration of UOS opening and minimum IBP would be observed across genders during swallowing across bolus volumes. The results indicate both of these hypotheses can be partially accepted. Statistically significant differences in CSA and IBP were observed during distension testing; however these differences were not detected across all balloon volumes (1 and 5ml volume for CSA and 1, 5, 10 and 15ml volumes for IBP). Similarly for UOS opening during swallowing, UOS diameter was significantly different across genders at baseline and during dry swallowing only. Duration of UOS opening was not different across groups across any bolus volume (i.e., dry, 5ml or 10ml liquid swallow) and IBP was significantly different on 5 and 10ml bolus volumes only. These findings will be discussed further in Chapter 5.

Results of the effect of postures and manoeuvres frequently employed in clinical practice on UOS opening during swallowing as measured by EndoFLIP® will be presented next.

4.2.4. EndoFLIP® evaluation of postures and manoeuvres to improve UOS opening during swallowing in an adult healthy group

Data from 385 swallows (one dry and two 5ml & 10ml liquid swallows across 7 conditions per subject or 5 x 7 x 11) was analysed from eleven subjects to obtain mean measures of UOS diameter, duration of UOS opening and minimum IBP across swallow events (see Table 4.7). To view postures and manoeuvres within study protocol being executed during swallowing across bolus volumes, see Figure 4.23 and Audio-Visual Clip 4 in Appendix 7.

Table 4.7 EndoFLIP® Measures of UOS Opening across Postures and Manoeuvres (n=11)

	UOS Diameter (mm) Mean (SD)			UOS Opening Duration (secs) Mean (SD)			Minimum IBP (mmHg) Mean (SD)		
	Dry Swallow	**5ml liquid**	**10ml liquid**	**Dry Swallow**	**5ml liquid**	**10ml liquid**	**Dry Swallow**	**5ml liquid**	**10ml liquid**
Head Neutral	9.26 (0.76)	8.36 (1.21)	8.37 (0.98)	0.43 (0.18)	0.47 (0.08)	0.48 (0.15)	4.61 (5.86)	4.73 (3.82)	4.92 (3.54)
Chin Tuck	7.49 (0.83)	7.74 (0.90)	8.08 (1.18)	0.37 (0.18)	0.43 (0.16)	0.48 (0.14)	4.59 (4.03)	5.37 (4.42)	5.60 (4.18)
Effortful Swallow	8.66 (1.51)	8.07 (1.01)	7.63 (1.03)	0.45 (0.14)	0.49 (0.17)	0.45 (0.10)	-2.06 (8.19)	0.64 (5.34)	1.40 (5.70)
Head Turn Left	8.61 (1.40)	7.62 (0.93)	7.60 (0.83)	0.41 (0.14)	0.40 (0.11)	0.48 (0.13)	2.29 (3.79)	3.58 (3.48)	3.99 (3.94)
Head Turn Right	7.77 (1.53)	7.49 (1.01)	7.33 (0.98)	0.35 (0.13)	0.45 (0.13)	0.43 (0.14)	-0.35 (4.25)	0.89 (3.54)	1.32 (3.97)
Mendelsohn manoeuvre	8.23 (1.52)	8.12 (1.38)	7.99 (1.52)	0.57 (0.20)	0.61 (0.17)	0.56 (0.18)	1.36 (8.24)	1.17 (7.69)	3.10 (8.80)
Supraglottic Swallow	7.78 (1.81)	7.18 (1.07)	7.47 (1.52)	0.44 (0.17)	0.50 (0.13)	0.52 (0.17)	0.11 (7.39)	-0.42 (6.56)	0.92 (5.59)

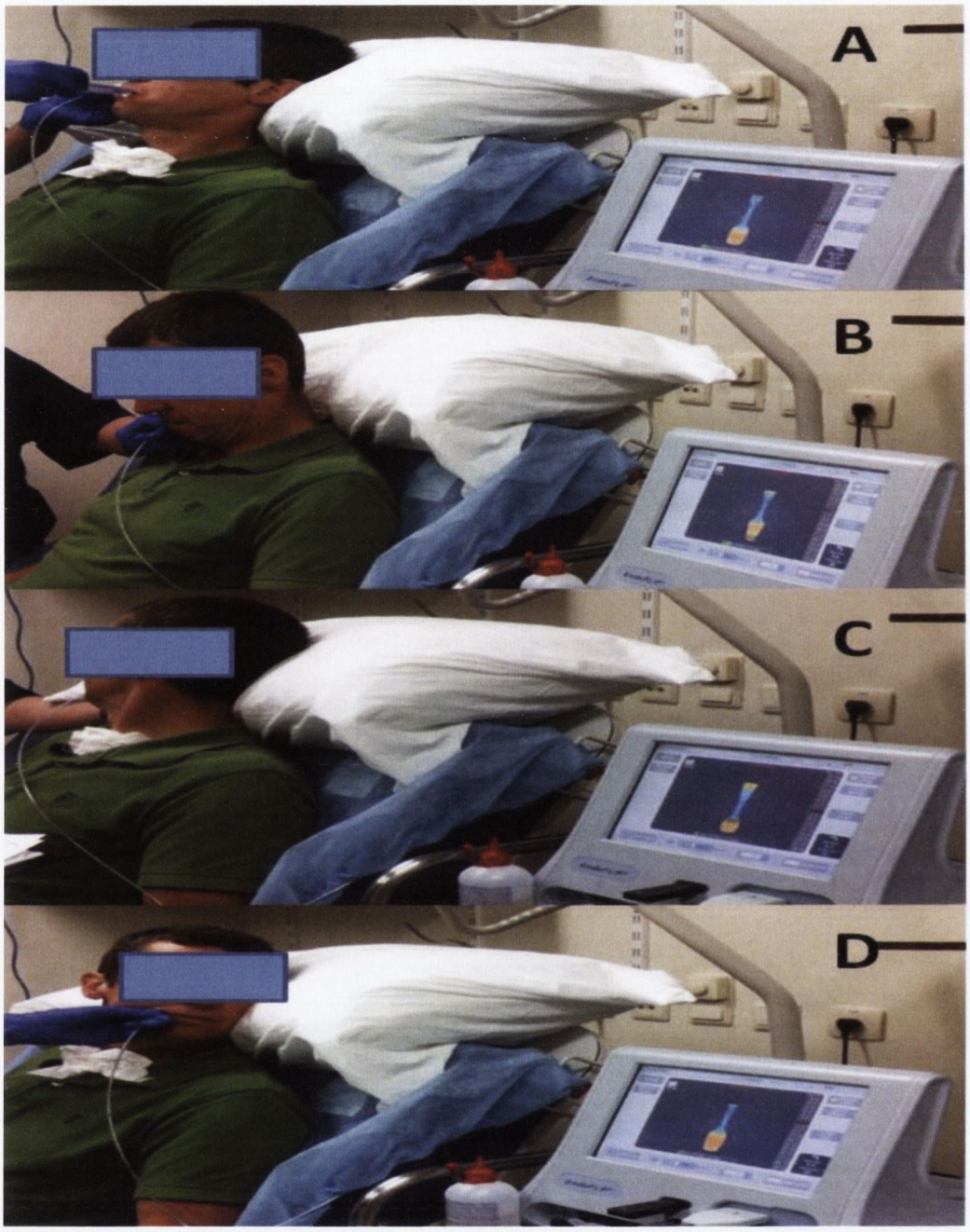

Figure 4.23 Subject completing Postures and Manoeuvres with EndoFLIP® Balloon Positioned in the UOS

The effect of postures and manoeuvres on UOS diameter during swallowing, irrespective of volume (i.e., volume not stratified), was statistically significant (p=0.0126). Mean extent of UOS opening (mm) during swallowing in head neutral position (8.62mm) was significantly larger than UOS opening during head turn right posture (7.54mm; p=0.0065) and UOS opening during supraglottic swallow (7.48mm; p=0.0035) (Figure 4.24). A trend toward statistical significance was also observed between extent of UOS opening in head neutral position (8.62mm) and UOS opening during chin tuck posture (7.85mm) (p=0.0854) (Table 4.8).

The duration of UOS opening during swallowing was also significantly affected by postures and manoeuvres irrespective of volume (p=0.0013). Mean duration of UOS opening during swallowing increased significantly from head neutral position (0.46 secs) to during the Mendelsohn manoeuvre (0.57 secs) (p=0.014) (See Figure 4.25).

Minimum IBP during swallowing was also significantly affected by postures and manoeuvres (p=0.0049). Specifically, a statistically significant difference in minimum IBP was detected between head neutral swallows (4.55mmHg) and supraglottic swallows (-0.13mmHg) (p=0.0225) (Figure 4.26). A trend towards statistical significance was noted between minimum IBP during head neutral (4.55mmHg) and minimum IBP during head turn right swallows (0.74mmHg) (p=0.0874) and between head neutral swallows (4.55mmHg) and effortful swallows (0.53mmHg) (p=0.0642).

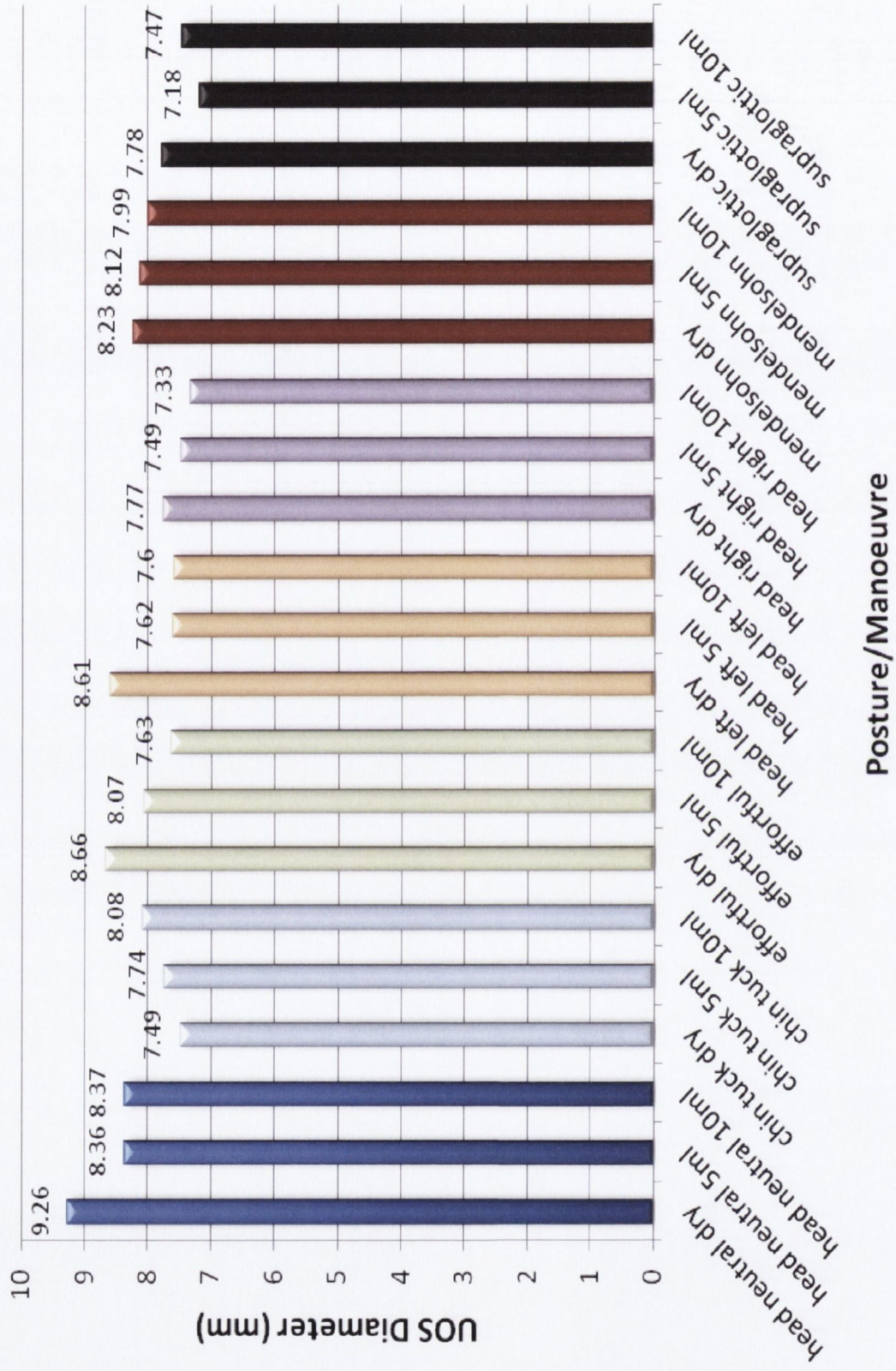

Figure 4.24 Extent of UOS Opening across Postures and Manoeuvres

Table 4.8 Effects of Postures and Manoeuvres on EndoFLIP® Measures of UOS Opening

EndoFLIP® Measure	Condition	Mean	Main Effect	Specific postures & manoeuvres (post-hoc adjusted p-value)	Post-hoc trend in adjusted p value
UOS Diameter (mm)	Head neutral	8.62 mm	p=0.0126	Head neutral-head turn right (p=0.0065) Head neutral- supraglottic (p=0.0035)	Head neutral-Chin tuck (p=0.0854)
	Chin tuck	7.85 mm			
	Effortful	8.09 mm			
	Head left	7.89 mm			
	Head right	7.54 mm			
	Mendelsohn	8.14 mm			
	Supraglottic	7.48 mm			
UOS Duration (secs)	Head neutral	0.46 secs	p=0.0013	Head neutral- Mendelsohn (p=0.0144)	N/A
	Chin tuck	0.43 secs			
	Effortful	0.45 secs			
	Head left	0.42 secs			
	Head right	0.42 secs			
	Mendelsohn	0.57 secs			
	Supraglottic	0.49 secs			
Min IBP (mmHg)	Head neutral	4.55 mmHg	p=0.0049	Head neutral- supraglottic (p=0.0225)	Head neutral- head turn right (p=0.0874) Head neutral-effortful (p=0.0642)
	Chin tuck	5.17 mmHg			
	Effortful	0.53 mmHg			
	Head left	3.41 mmHg			
	Head right	0.74 mmHg			
	Mendelsohn	1.66 mmHg			
	Supraglottic	-.13 mmHg			

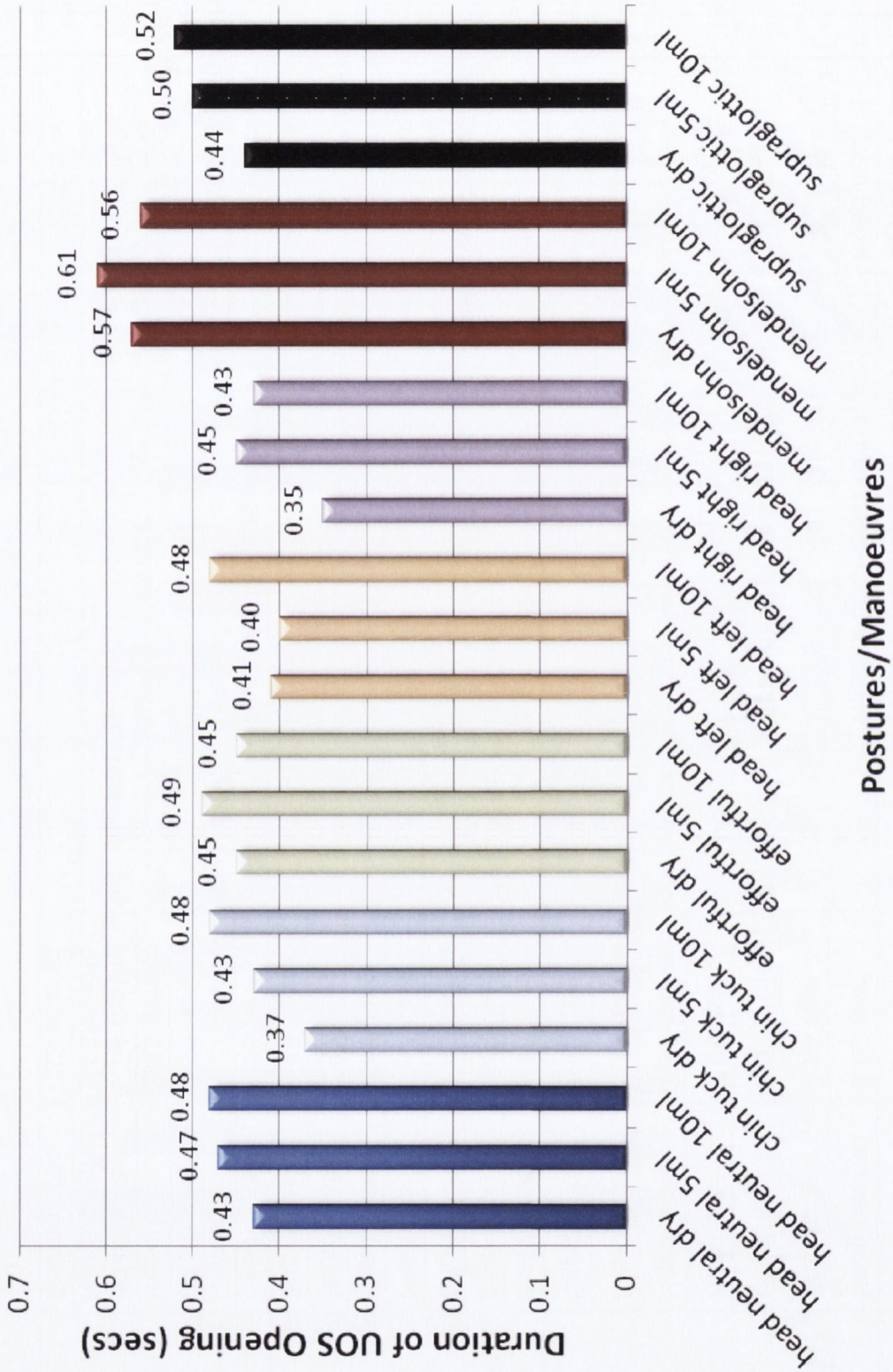

Figure 4.25 Duration of UOS Opening across Postures and Manoeuvres

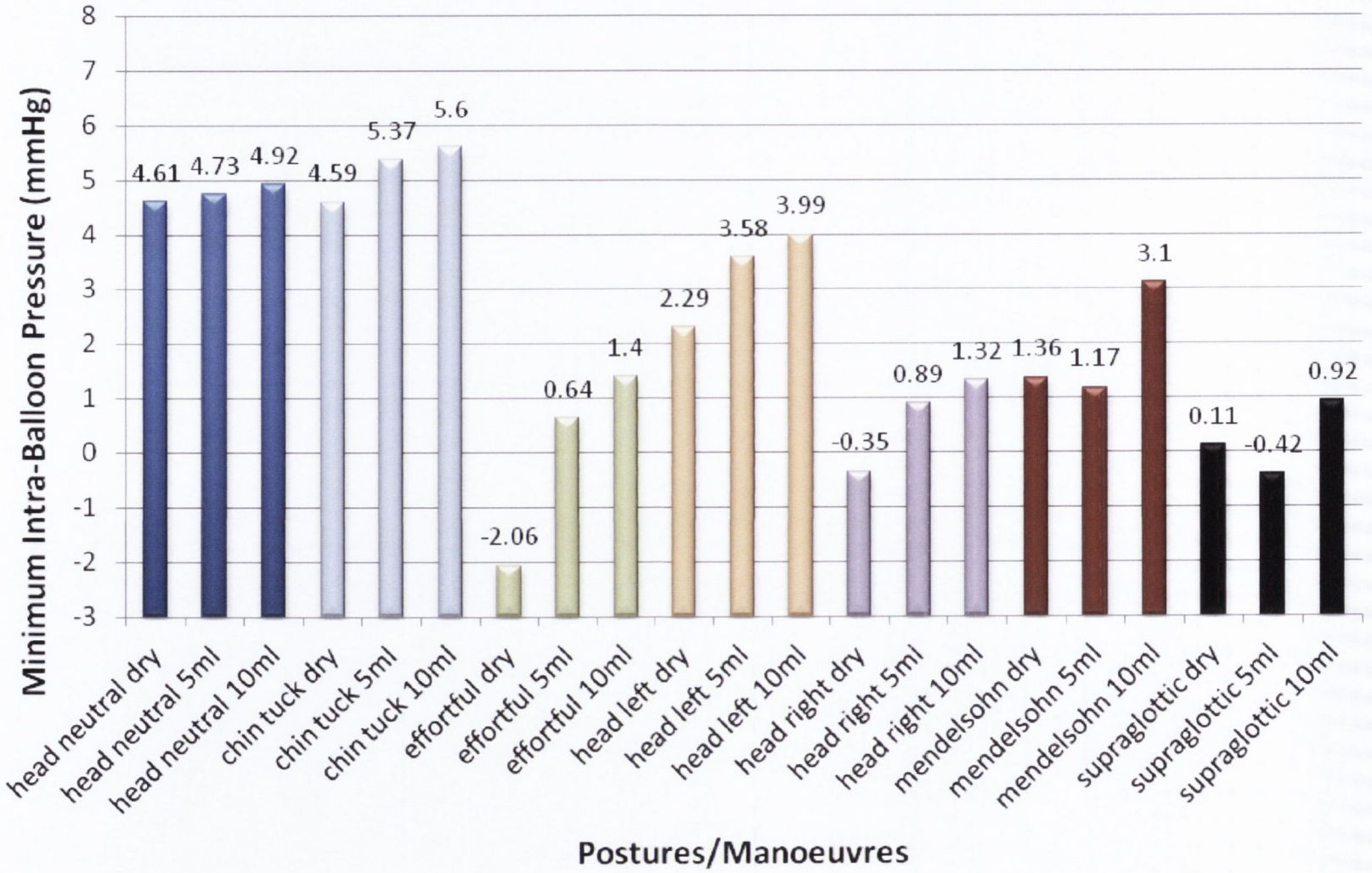

Figure 4.26 Minimum IBP across Postures and Manoeuvres

The alternative hypothesis for this study was that voluntary postures and manoeuvres commonly employed in dysphagia practice (chin tuck, head turn left and right, effortful swallow, Mendelsohn manoeuvre, supraglottic swallow) would alter the extent and duration of UOS opening during swallowing events and alter drop in IBP at rest and during dry, 5ml and 10ml liquid swallowing in an adult healthy group. Based on the statistically significant changes in extent and duration of UOS opening during swallowing and the statistically significant alteration in minimum IBP during swallowing, this hypothesis can be accepted.

The results from this study will be discussed in detail in Chapter 5. Next, results of the third research question comparing EndoFLIP® measures of UOS opening to AIM analysis data will be reported.

4.3. Research Question 3: Comparison of EndoFLIP® measures of UOS opening during swallowing to high resolution manometry with impedance

All subjects co-operated and tolerated both procedures well and there were no complications as a result of either assessment. To view a segment of the HRM-MII study protocol being executed, see Audio-Visual Clip 5 in Appendix 7. Significant correlations (Spearman's Rho) between EndoFLIP® and AIM analysis parameters are detailed in Table 4.9.

Table 4.9 Initial Correlations between EndoFLIP® and AIM Analysis Data

	Vol	HRM-MII parameter	Spearman's Rho	P value
EndoFLIP® UOS Diameter	**Dry**	PNadImp	-.818	**0.0038***
	5ml	Flow Interval	-0.609	**0.0467***
	10ml	Nil	-	-
EndoFLIP® UOS Open Duration	**Dry**	Relaxation Interval (RI)	-0.7277	**0.017***
		Intra-Bolus Pressure	-0.69	**0.027***
	5ml	Swallow Risk Index	0.6834	**0.02***
		tnadimp-peakp	-0.5735	0.065 (trend only)
	10ml	nil	-	-
EndoFLIP® Min Pressure	**Dry**	TNadImp-PeakP	-0.842	**0.0022***
	5ml	UOS- NadP	-0.55	0.0793 (trend only)
	10ml	Nil	-	-

Any statistically significant correlations found were included in the mixed model analysis. This analysis checked for a main effect, a volume dependent effect and an interaction effect within the data (see Table 4.10).

4.3.1. EndoFLIP® UOS Diameter

Based on mixed regression analysis, there was a trend towards a significant main effect correlation between EndoFLIP® UOS diameter (mm) and PNadImp (p=0.061). A significant volume dependent effect was observed (p=0.0018), which was significant on dry (p=0.0155) and 5ml liquid (p=0.0239) swallows. A significant interaction effect was also observed between these two variables (p=0.0341; 0-5ml volumes: p=0.0145).

A trend towards a significant interaction effect was observed between EndoFLIP® measure of UOS diameter and Flow Interval (F=3.46; p=0.0721). A volume dependent effect was observed between EndoFLIP® UOS diameter and intra-balloon pressure (p=0.0546). No effect was detected between EndoFLIP® UOS diameter and TNadImp-PeakP (Table 4.10).

4.3.2. EndoFLIP® UOS Opening Duration

A significant volume dependent effect was observed between EndoFLIP® UOS Opening Duration and TNadImp-PeakP (F=5.30; p=0.0269) which was significant on 5ml liquid swallows (p=0.0117). A trend towards a significant interaction effect was also observed between these two parameters (F=3.55; p=0.0686) (5ml-10ml volumes: p=0.0716) (Table 4.10). A significant interaction effect correlation was observed between duration of UOS opening from EndoFLIP® and RI (p=0.0272; 0-5ml volumes: p=0.0098).

4.3.3. EndoFLIP® Minimum IBP

Based on the mixed model analysis, no main effect correlations were observed between EndoFLIP® measures of IBP and AIM analysis parameters (i.e., Tnadimp-PeakP, UOS-NadP or UOS Resistance) (Table 4.10).

Table 4.10. Correlations between EndoFLIP® and AIM Analysis Measures of UOS Opening based on Mixed Model Analysis[19]

EndoFLIP® Measure	AIM Analysis Measure	Main Effect Correlation (correlation irrespective of dry, 5ml or 10ml volume)	Volume Dependent Effect Correlation (correlation observed on a specific volumes)	Interaction Effect Correlation (correlation is dependent on volume given)
UOS Diameter (mm)	**PNadImp**	p=0.061*	**p=0.0018**** (dry p=0.0155; 5ml p=0.0239)	**p=0.0341**** (0-5ml volumes: p=0.0145)
	TNadImp-PeakP	p=0.88	p=0.98	p=0.7263
	Flow Interval	p=0.3292	p=0.1734	p=0.0721*
	IBP	p=0.4674	p=0.0546*	p=0.2723
UOS Opening Duration (secs)	**TNadImp-PeakP**	p=0.4576	**p=0.0269**** (5ml volume p=0.0117)	p=0.0686*
	RI	p=0.379	p=0.0538*	**p=0.0272**** (0-5ml volumes: p=0.0098)
	Resistance	p=0.1996	p=0.3427	p=0.0995*
	Intra-Bolus Pressure	p=0.6198	p=0.2695	p=0.075*
	Swallow Risk Index	p=0.6279	p=0.9015	p=0.3029
Minimum IBP (mmHg)	**TNadImp-PeakP**	p=0.4827	p=0.994	p=0.8923
	NadP	p=0.2061	Not tested	Not tested
	UOS Resistance	P=0.1649	Not tested	Not tested

[19] **= statistically significant (i.e. < 0.05). Post-hoc p-values are in parentheses. *= trend towards significance (i.e. 0.05-0.1).

In this study, the alternate hypothesis was that EndoFLIP® temporal, diameter and pressure measures of UOS opening during swallowing would significantly correlate with data obtained from AIM analysis using combined HRM-MII in a group of healthy adults. EndoFLIP® diameter and temporal measures did correlate significantly with AIM analysis data; therefore these alternate hypotheses can be accepted. However, EndoFLIP® IBP data did not correlate significantly with AIM analysis data and hence this hypothesis is rejected.

This study served as a starting point in establishing the diagnostic accuracy of EndoFLIP® measures of UOS opening during swallowing. These results will be discussed in detail in Chapter 5. Next, results of studies establishing the clinical utility of EndoFLIP® in dysphagia practice will be presented.

4.4. Research Question 4: Clinical utility of EndoFLIP® in dysphagia practice

To address this fourth and final key research question, two sub-questions were addressed. The results associated with these two questions are described below.

4.4.1. Clinical utility of EndoFLIP® in a population of people with known UOS dysfunction

Of the ten subjects with laryngectomy recruited for this study, seven tolerated passing of the EndoFLIP® probe into the oesophagus and positioning of the balloon in the POS. In three cases (Subjects 6, 8 and 9), the EndoFLIP® probe could be passed trans-nasally but it could not be passed through the POS region during trans-nasal insertion of the EndoFLIP®. Of note, two of these three subjects had a history of strictures and or stenosis in the POS region and two had a history of upper oesophageal dilation procedures to widen the POS region post radiation. These three patients also had marked difficulty swallowing and had difficulty initiating dry swallows to allow the catheter to be passed into the oesophagus.

4.4.1.1. POS Distensibility

Of the seven patients with total laryngectomy who completed distensibility testing, a narrowing was observed in the geometric profile of the POS across all studies when the balloon was in position. However, this narrowing differed from the distinct hourglass shape of the UOS previously observed in healthy control studies. The POS appeared to have a wider resting diameter and the segment was longer in laryngectomy patients. Representative geometric profiles of the POS on the EndoFLIP® screen in clinical studies at 20ml balloon volume are compared to the hourglass shape of the UOS observed in healthy adults in Figure 4.27.

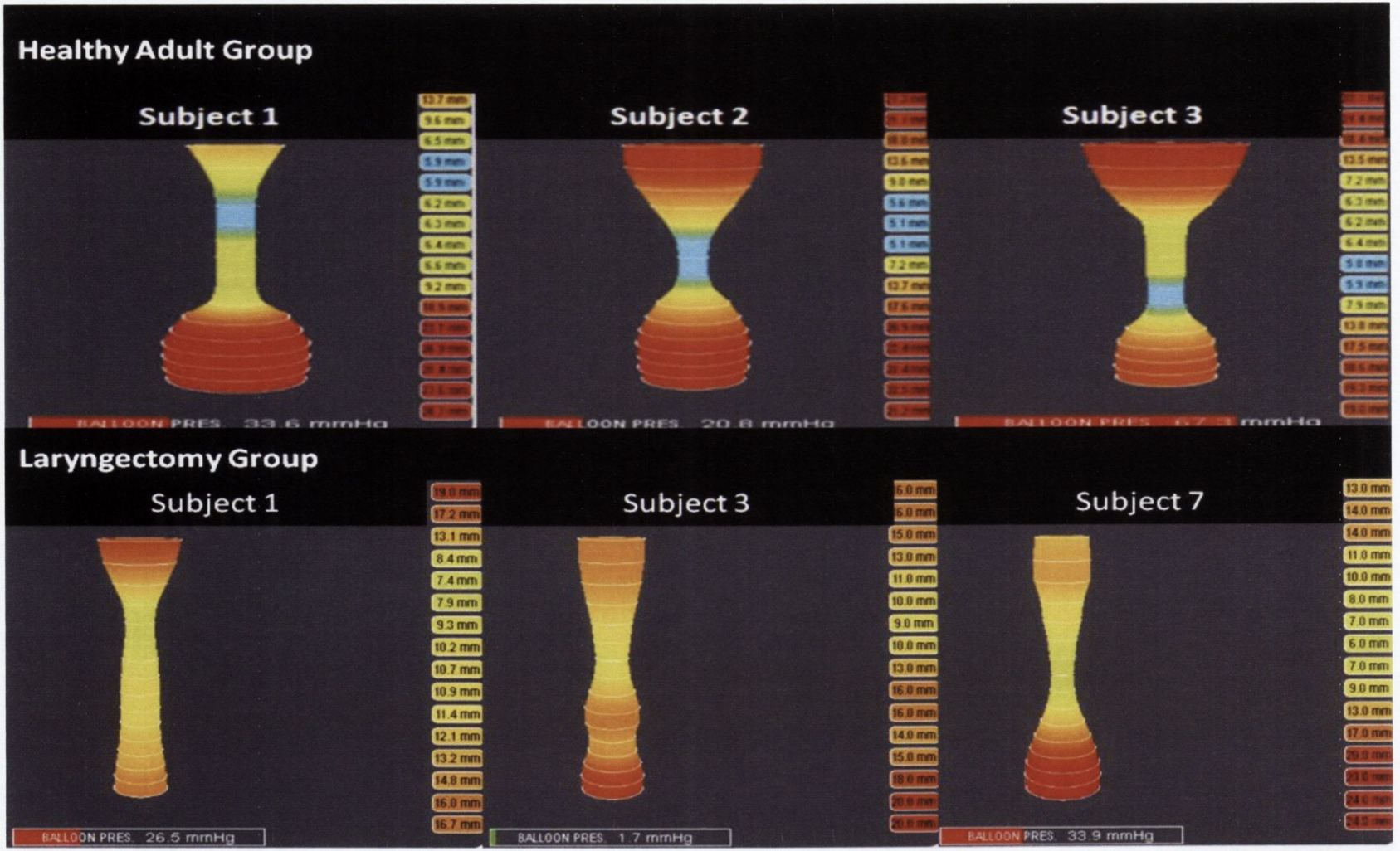

Figure 4.27 Differences in Geometric Profiles of UOS Region between Healthy Adults and Subjects with Total Laryngectomy

POS Cross-Sectional Area

The minimum POS CSA increased significantly during the 20ml ramp distension in the laryngectomy group (n=7) ($p<.001$). A statistically significant increase in CSA was observed from 1ml to 5ml balloon volume ($Z=-2.814$, $p=0.005$); from 5ml to 10ml balloon volume ($Z=-2.803$, $p=0.005$); from 10ml to 15ml balloon volume ($Z=-2.803$, $p=0.005$) and from 15ml to 20ml balloon volume ($Z=-2.803$, $p=0.005$) (Table 4.11 & Figure 4.28).

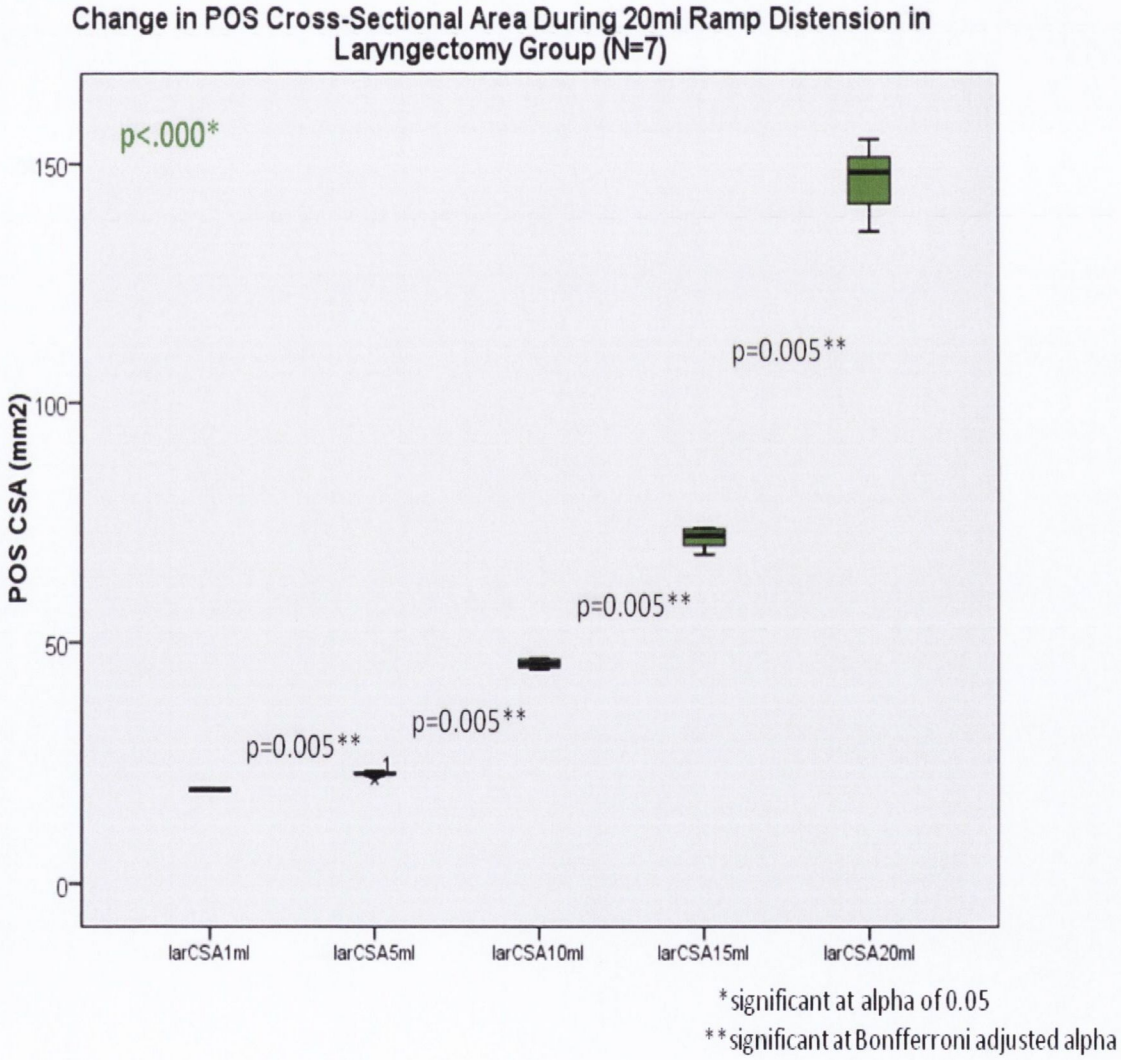

Figure 4.28 Change in POS CSA during 20ml Ramp Distension in Total Laryngectomy Group (n=7)

Table 4.11 Change in EndoFLIP® Measures during 20ml Ramp Distension in Total Laryngectomy Group (n=7)

		Min	Max	Percentiles			Kruskal- Wallis	Wilcoxon tests
				25th	50th (Median)	75th		
	POS CROSS-SECTIONAL AREA							
Balloon Volumes (mls)	1	19.47	19.47	19.47	19.47	19.47	p<0.001	1-5ml: p=0.005
	5	21.64	23.32	22.66	22.81	22.98		5-10ml: p=0.005
	10	44.45	46.74	44.82	45.61	46.55		10-15ml: p=0.005
	15	68.29	73.91	70.02	72.26	73.60		15-20ml: p=0.005
	20	135.95	155.18	141.12	148.31	151.94		
	INTRA-BALLOON PRESSURE							
Balloon Volumes (mls)	1	16.20	19.00	16.85	18.40	18.69	p<0.001	1-5ml:p=0.005
	5	15.89	16.60	16.14	16.33	16.55		5-10ml: p=0.005
	10	14.45	14.96	14.68	14.79	14.90		10-15ml: p=0.445
	15	13.89	15.62	13.10	14.46	15.07		15-20ml: p=0.005
	20	15.81	17.29	16.11	16.49	17.16		

Minimum IBP

The minimum IBP also altered significantly during the 20ml ramp distension ($p<.001$). A statistically significant decrease in IBP was observed from 1ml to 5ml balloon volume ($Z=-2.803$, $p=0.005$) and from 5ml to 10ml balloon volume ($Z=-2.803$, $p=0.005$). No statistically significant difference in IBP was identified between 10ml and 15ml balloon volumes ($Z=-.764$, $p=0.445$). However, there was a statistically significant increase in IBP from 15ml to 20ml balloon volumes ($Z=-2.803$, $p=0.005$) (Table 4.11 & Figure 4.29).

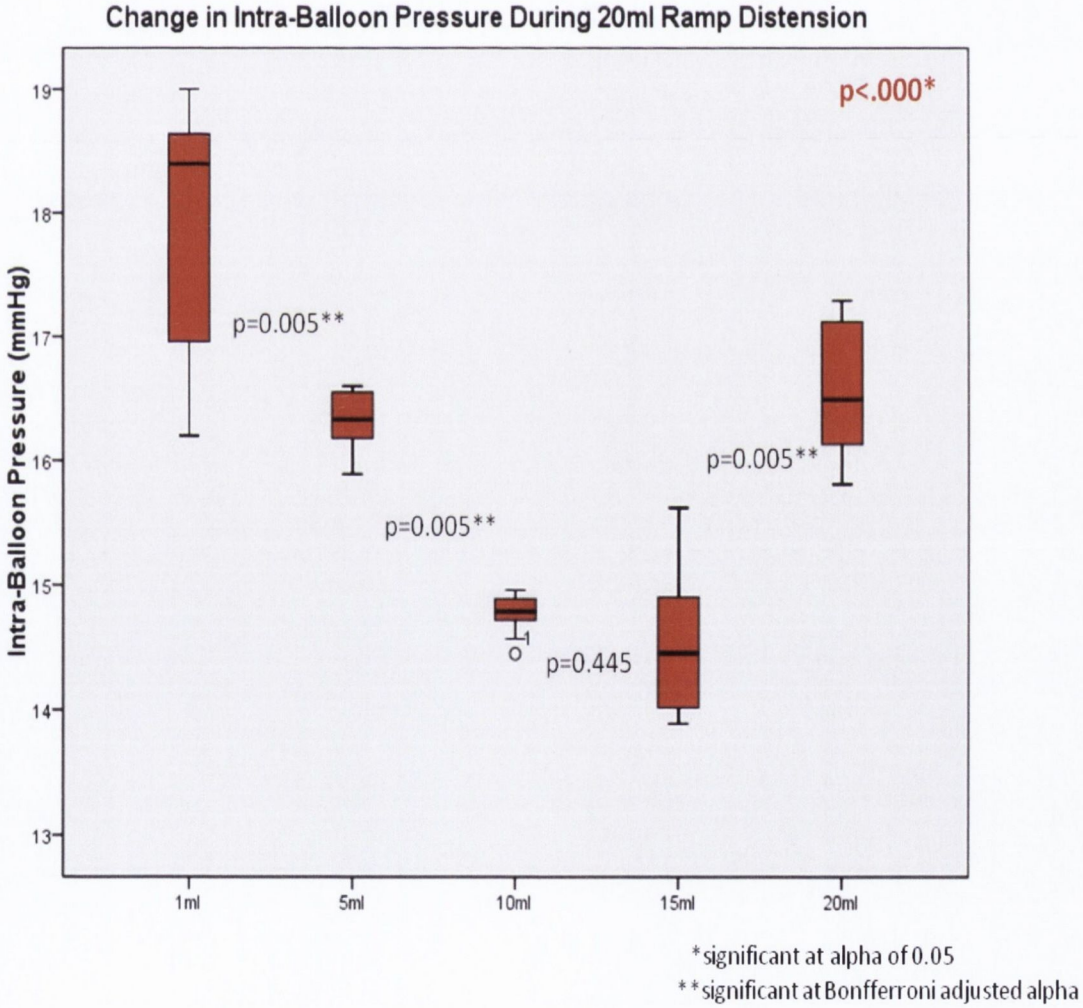

Figure 4.29 Change in IBP during 20ml Ramp Distension in Total Laryngectomy Group (n=7)

Distensibility- Total Laryngectomy versus Healthy Adult Group

Distensibility findings from the laryngectomy group (n=7) were subsequently compared to data from a previously studied group of healthy subjects (n=13). A significant difference in UOS CSA was evident between laryngectomy and control groups at 1ml, 5ml, 10ml, 15ml and 20ml volumes during the ramp distension (see Table 4.12). CSA was higher at each volume within the total laryngectomy group. In fact, POS CSA increased to 148mm^2 during distensibility testing in the laryngectomy group, whereas the UOS opened to just 23.71mm^2 in the control group. In contrast, IBP was lower at 1ml, 5ml and 10ml balloon volumes in the control group but it increased substantially during distensibility testing. In the total laryngectomy group, IBP decreased during distensibility testing and was significantly lower than the control group at 15ml and 20ml balloon volumes (Figure 4.30).

Table 4.12 Differences in EndoFLIP® Measures of Distensibility between Total Laryngectomy and Control Groups[20]

	Balloon Volume (ml)	Laryngectomy Group Median (IQR) (n=7)	Control Group Median (IQR) (n=13)	Wilcoxon Signed ranks test (z)	p value
CSA (mm2)	1	19.47 (0)	18.54 (0)	-3.162	.002*
	5	22.81 (0.32)	18.69 (0.09)	-2.807	.005*
	10	45.61 (1.73)	24.23 (6.01)	-2.701	.007*
	15	72.26 (3.58)	21.19 (4.37)	-2.803	.005*
	20	148.31 (10.82)	23.71 (1.94)	-2.803	.005*
IBP (mmHg)	1	18.40 (1.84)	6.79 (0.78)	-2.803	.005*
	5	16.33 (0.41)	9.41 (5.95)	-2.499	.012*
	10	14.79 (0.22)	7.12 (7.38)	-2.599	.009*
	15	14.46 (1.07)	36.12 (21.09)	-2.803	.005*
	20	16.49 (1.05)	45.635 (11.58)	-2.803	.005*

[20] *=statistically significant ($p<0.05$)

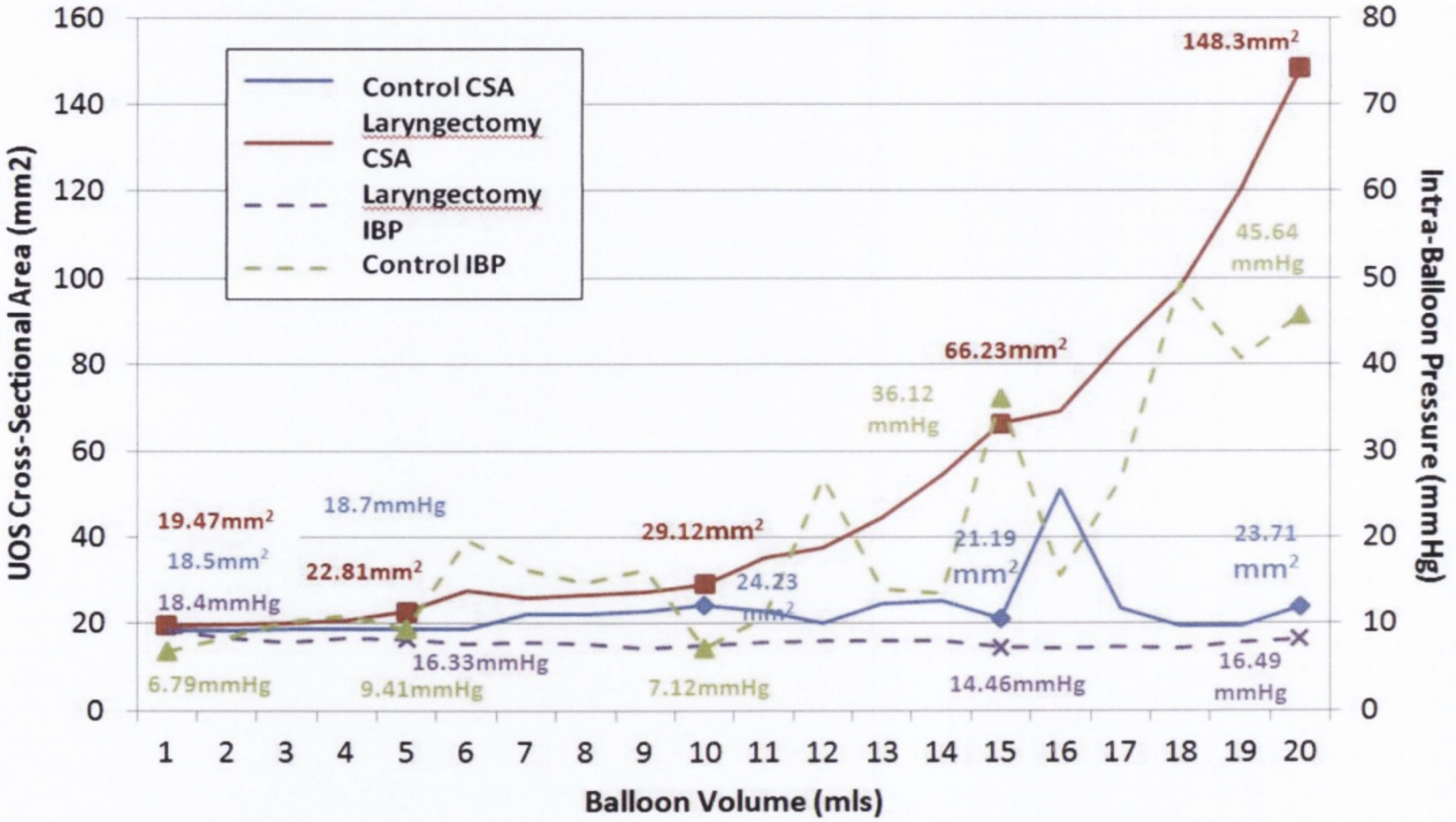

Figure 4.30 Changes in POS and UOS CSA and IBP during 20ml Ramp Distension in Total Laryngectomy (n=7) and Control Groups (n=13)

4.4.1.2. POS Opening during Swallowing

Three POS opening during swallowing measurements obtained from EndoFLIP® are presented below.

POS Diameter

A statistically significant change in POS diameter was detected across swallow events (baseline, dry, 5ml and 10ml liquid swallowing) in the total laryngectomy group (n=7) (p=0.002). During dry swallowing, POS diameter significantly increased from a baseline of 5.05mm to 7.36mm (p=0.018). While median POS diameter was largest for 10ml swallows (7.65mm), any difference in POS diameter between dry and 5ml swallowing (p=0.398), dry and 10ml swallows (p=0.735) and 5ml and 10ml swallowing (p=0.398) was not statistically significant (Table 4.13 & Figure 4.31).

Minimum IBP

There was no statistically significant change in IBP across swallow events (baseline, dry, 5ml and 10ml liquid swallowing) in the total laryngectomy group (n=7) (p=0.897) (Table 4.13 & Figure 4.31).

Duration of POS Opening

No statistically significant difference in duration of POS opening across swallow events (baseline, dry, 5ml and 10ml liquid swallowing) was observed in the total laryngectomy group (n=7) (p=0.656) (Table 4.13 & Figure 4.31).

Table 4.13 EndoFLIP® Measures of POS Opening during Swallowing in Total Laryngectomy Group (n=7)

	Minimum POS Diameter (mm)				Minimum IBP (mmHg)				POS Opening Duration (secs)		
No.	base	dry	5ml liquid	10ml liquid	base	dry	5ml liquid	10ml liquid	dry	5ml liquid	10ml liquid
1	4.98	7.26	7.09	7.65	25.53	24.84	25.21	21.17	4.8	7.1	2.3
2	5.03	10.25	10.5	9.88	4.68	6.91	6.25	5.28	1.6	0.7	1.2
3	5.08	6.58	6.82	7.2	-.43	9.07	0.91	-3.04	1.4	0.5	2.2
4	4.95	8.82	10.65	8.45	28.07	25.75	27.73	29.96	0.6	0.6	0.5
5	5.15	6.71	5.59	6.78	12.17	15.33	10.58	8.68	1	2	1.8
6	5.05	9.53	10.11	9.45	40.17	27.71	26.57	24.48	0.8	0.9	1.6
7	5.39	7.36	7.26	6.15	35.64	34.75	33.17	33.8	0.9	0.8	.7
Median	**5.05**	**7.36**	**7.26**	**7.65**	**25.53**	**24.84**	**25.21**	**21.17**	**1**	**0.8**	**1.6**
IQR	**0.17**	**2.82**	**3.68**	**2.67**	**30.68**	**18.64**	**21.05**	**24.68**	**1.8**	**1.4**	**1.5**

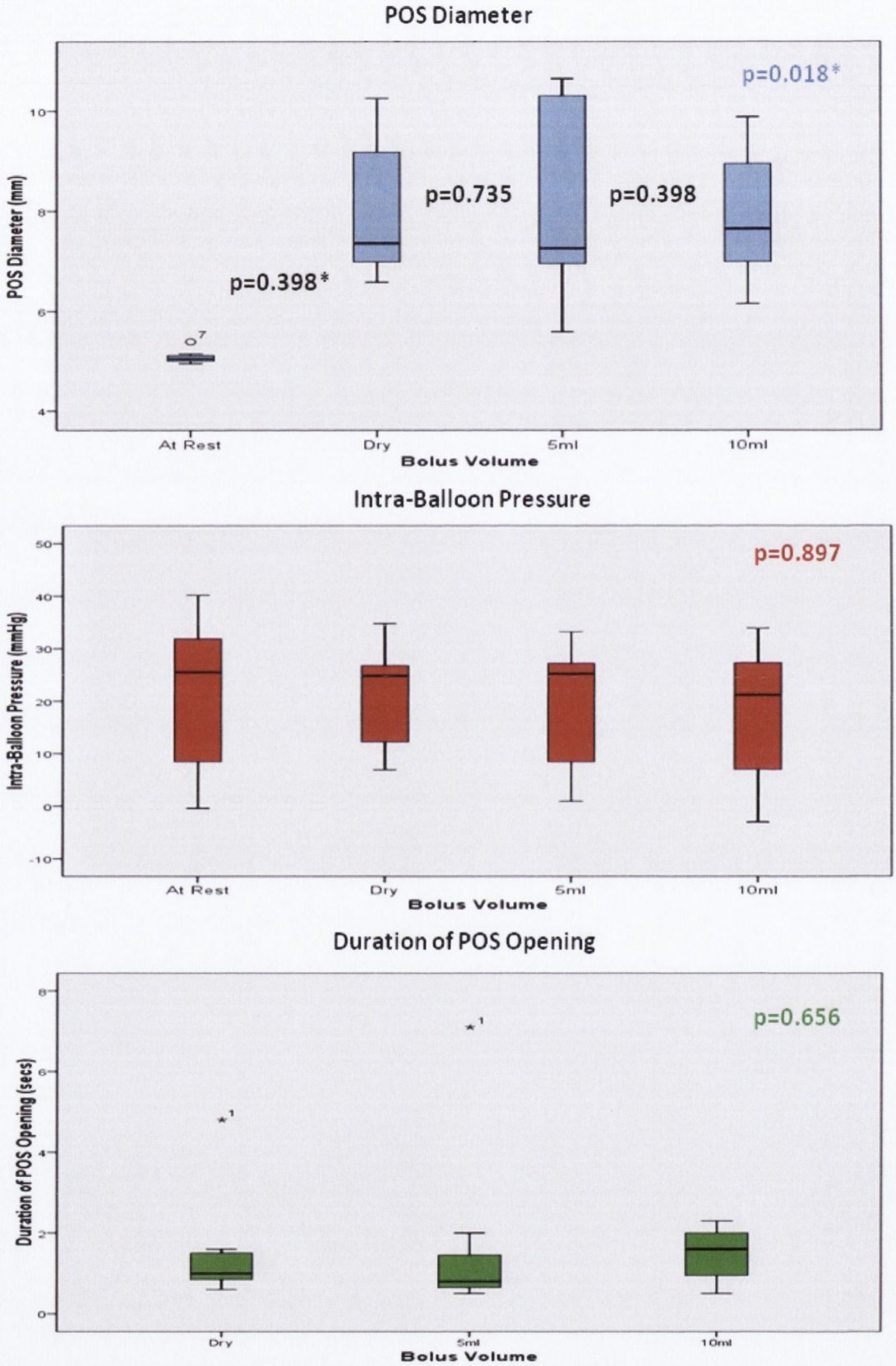

Figure 4.31 Changes in EndoFLIP® Measures of Swallowing in Total Laryngectomy Group (n=7)

Swallowing- Total Laryngectomy versus Healthy Controls

At rest, the narrow region of the POS in total laryngectomy patients was significantly wider (5.05mm) than the UOS in control subjects (4.9mm) ($p=0.018$). Despite this, UOS diameter was wider during dry, 5ml and 10ml liquid swallowing in healthy controls compared to POS opening in patients with total laryngectomy. However, these differences were not statistically significant (Table 4.14).

There was not a significant difference in median IBP at rest between subgroups at a 12ml balloon volume. During dry, 5ml and 10ml liquid swallowing, median minimum IBP was lower in control subjects compared to total laryngectomy patients. However, these differences were not statistically significant.

Duration of POS opening was significantly longer across dry ($p=0.028$), 5ml ($p=0.034$) and 10ml ($p=0.027$) liquid swallows in the total laryngectomy group compared to duration of UOS opening in healthy controls (Table 4.14) (Figure 4.32).

Results indicate that there was a statistically significant increase in POS CSA, but not IBP, during distensibility testing. During dry and liquid swallowing, POS diameter increased significantly from baseline and IBP decreased significantly. Statistically significant differences in CSA and IBP were observed during distensibility testing between the total laryngectomy group and healthy controls and significant differences in extent and duration of sphincter opening and in minimum IBP during swallowing were also detected between the total laryngectomy group and healthy controls. The hypotheses for this study can therefore be accepted. These results will be discussed in detail in Chapter 5.

Table 4.14 Differences in EndoFLIP® Measures of POS and UOS Opening during Swallowing between Total Laryngectomy (n=7) and Control Groups (n=13)[21]

	Median Minimum POS/ UOS Diameter (mm)			**Median Minimum IBP (mmHg)**			**Median POS Opening Duration (secs)**		
	laryngectomy	control	p value	laryngectomy	control	p value	laryngectomy	control	p value
Base-line	5.05	4.9	**0.018***	25.53	18.8	0.866			
Dry	7.36	9.6	**0.063**	24.84	3.6	**0.063**	1.0	0.5	**0.028***
5ml	7.26	8.61	0.735	25.21	4.8	0.128	0.8	0.5	**0.034***
10ml	7.65	8.27	0.237	21.17	2.96	0.128	1.4	0.5	**0.027***

[21] *=statistically significant ($p<0.05$)

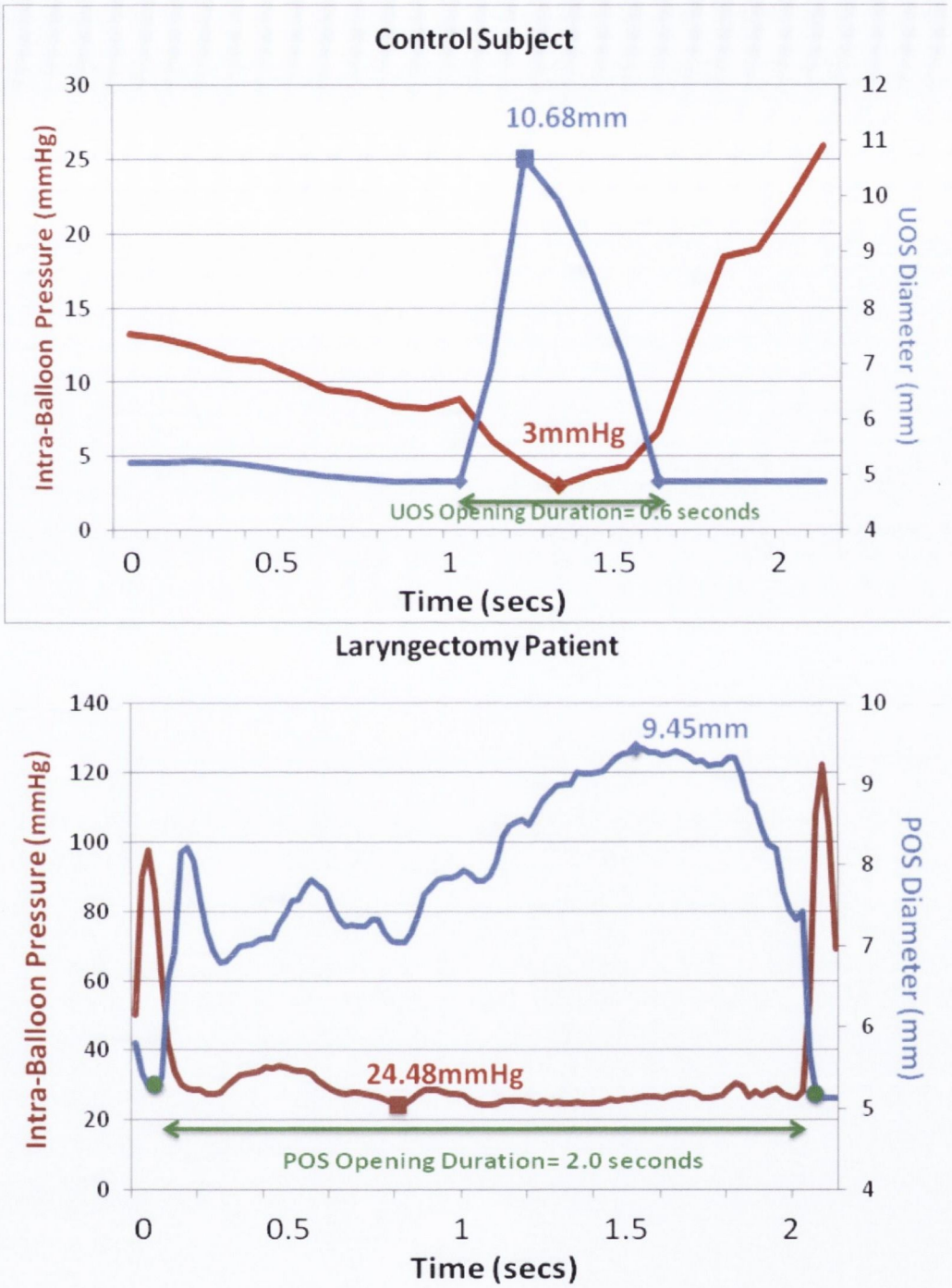

Figure 4.32 Differences in EndoFLIP® Measures during 10ml Liquid Swallow between Total Laryngectomy Patient and Control Subject

In the next section of this chapter, feedback from dysphagia clinicians internationally regarding satisfaction with current UOS evaluation and the potential role of EndoFLIP® in dysphagia practice will be described.

4.4.2. Satisfaction of dysphagia clinicians with current UOS evaluation and feedback on the potential role of EndoFLIP® in clinical dysphagia practice

A 25-item electronic survey was disseminated internationally to dysphagia clinicians to establish satisfaction levels with current UOS evaluations. Responses were obtained from 485 SLTs over the three-month period. A response rate could not be determined for the following reasons:

I. The survey was disseminated by SLTs in ROI and it was not possible to determine how many SLTs received the survey link. There is no national record in ROI regarding number of SLTs who have obtained postgraduate training to work in dysphagia.

II. Information on size of membership in UK Dysphagia SIGs could not be obtained and thus the number of SLTs who accessed the survey.

III. Number of ASHA Division 13 members using internet web forum could not be established.

Two hundred and thirty one (47.6%) of the responses received were incomplete and excluded from analysis leaving a total of 254 completed surveys eligible for analysis. Incomplete responses occurred as some SLTs were unable to access online video clips that formed part of the survey. Of the 254 completed responses, a further 30 were excluded as respondents did not have an active dysphagia caseload. A total of 224 surveys were suitable for analysis. In addition to establishing total group findings (n=224), a sub-group analysis was performed to explore differences in satisfaction and challenges across countries (USA n=69, UK n=63, ROI n=62) (n=194) and work settings (acute care n=147, rehabilitation n=23, community care n=40) (n=210). Smaller subgroups (i.e., third level education and private practice) were excluded from this analysis. Respondents were also divided according to level of clinical experience (1-10 years n=108, > 11 years n=115). Given the wide range of clinical experience within the total response group (0->20 years) as well as the large number of respondents with substantial clinical dysphagia experience, ten years was chosen as the cut-off point to categorise SLTs according the level of experience. This provided an opportunity to capture responses from a highly specialist international SLT group. Responses were also analysed according to

dysphagia caseload (0-59% n=78, 60-100% n=146) and nature of client group (adults n=170, paediatric/mixed n=54). Details regarding nationality and work settings of survey participants are in Table 4.15.

Table 4.15 Distribution of Respondents by Country and Work Setting

	n=224	Acute Care	Rehabilit-ation Setting	Community Care	Third level Ed.	Private Practice
Republic of Ireland (ROI)	27.7% (62)	61.3% (38)	8.1% (5)	27.4% (17)	0	3.2% (2)
United Kingdom (UK)	28.1% (63)	68.3% (43)	1.6% (1)	30.2% (19)	0	0
United States of America (USA)	30.8% (69)	71% (49)	15.9% (11)	1.4% (1)	10.1% (7)	1.4% (1)
Europe (outside Ireland/ UK)	4% (9)	44.4% (4)	22.2% (2)	0	0	33.3% (3)
Canada	4.9% (11)	54.5% (6)	27.3% (3)	18.2% (2)	0	0
Australia	2.7% (6)	83.3% (5)	16.7% (1)	0	0	0
New Zealand	1.8% (4)	50% (2)	0	25% (1)	25% (1)	0
Total	**224**	**65.6% (147)**	**10.3% (23)**	**17.9% (40)**	**3.6% (8)**	**2.7% (6)**

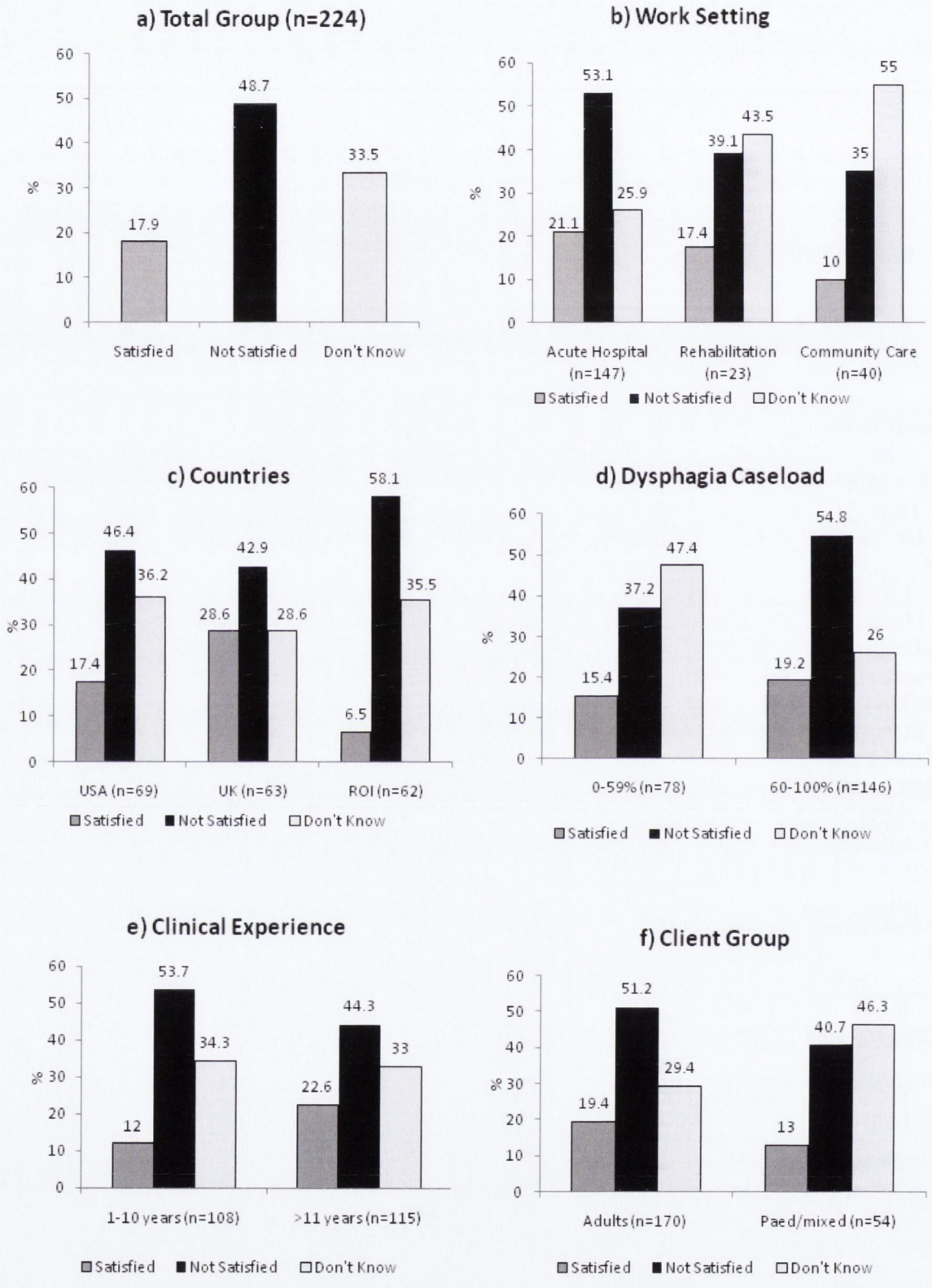

Figure 4.33 Satisfaction amongst SLTs with Current Methods to Evaluate UOS Opening

4.4.2.1. Satisfaction amongst SLTs with Current Methods Used to Evaluate UOS Function

Only 17.9% (40/224) of SLTs surveyed were satisfied with the accuracy and reliability of evaluations currently available to measure UOS function. Forty-nine percent of SLTs reported dissatisfaction with current UOS evaluation (Figure 4.33). SLTs most dissatisfied with current UOS evaluations included those working in acute hospital settings (53.1%, 78/147), those with large (60-100%) dysphagia caseloads (54.8%, 80/146) and SLTs working with adults (51.2%, 87/170). There was no significant association between satisfaction with current UOS evaluation and level of clinical experience (r= 0.078; p-value = 0.246) (Figure 4.34).

Figure 4.34 Satisfaction with Current UOS Evaluation according to Level of Clinical Experience

4.4.2.2. Challenges in UOS Evaluation

Eighty seven percent (195/224) of SLTs surveyed experience challenges in evaluating UOS opening during swallowing. Challenges were more evident from SLTs working with adults (86.5%, 147/170) and from respondents with more (>11 years) clinical experience (85.6%, 125/146). Challenges were also increased in rehabilitation settings (100%, 23/23), although highly prevalent in acute hospitals (85.7%, 126/147). The 195/224 SLTs who reported challenges in evaluating UOS dysfunction were subsequently asked to select the most prominent challenges experienced from six examples provided within the survey (see survey in Appendix 6). The most frequently selected challenges reported within this group (n=195) are detailed in Figure 4.35 and Table 4.16.

Lack of resources/equipment was the most frequently reported challenge reported by SLTs when evaluating UOS impairment in people with dysphagia (56%, 109/195) (Table 4.16). Availability of resources and equipment used to evaluate the UOS (i.e., VFS, FEES, PM and needle EMG) is presented in Table 4.17. VFS is accessible to over three quarters of respondents (78.9%, 176/224) and to 92.5% (136/147) of SLTs working in acute hospitals. Nevertheless, VFS availability is markedly reduced in ROI (59.7%, 37/62) and is available to just over one quarter (27.5%, 11/40) of SLTs working in community care.

FEES is available to less than half of SLTs surveyed (48.1%) (Table 4.17), with low access in rehabilitation (26.1%) and, in particular, in community care settings (2.6%) (Table 4.17). However, there was good access to FEES in acute care settings (62.6%) and from respondents working in USA (65.2%). Availability of physiological dysphagia evaluations (i.e., PM, needle EMG) was low across the response group (Table 4.17). PM was available to just 13.9% of SLTs, and to less than one fifth (18%) of SLTs working in acute care (Table 4.17). Just six percent of SLTs reported availability of needle EMG in UOS evaluation, which increased to 7.4% in acute care and to 13.6% availability in USA (Table 4.17).

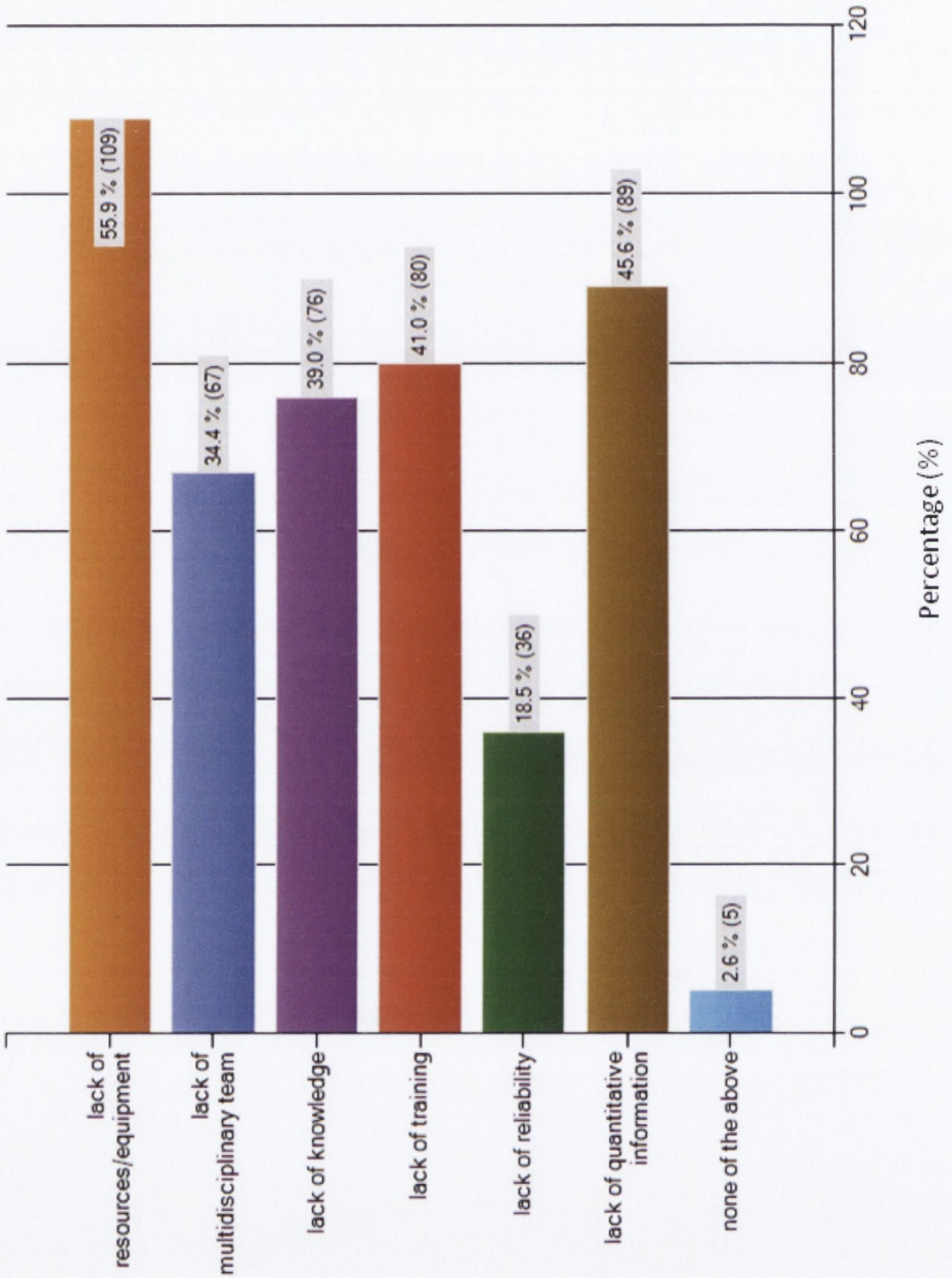

Figure 4.35 Biggest Challenges in the Investigation of UOS Dysfunction according to Survey Respondents

Table 4.16 Challenges encountered by SLTs in UOS Evaluation

		Lack of resources	Lack of MDT	Lack of knowledge	Lack of Training	Lack of reliability	Lack of quantitative information
	Total (n=195/224)[22]	55.9% (109)	34.4% (67)	39% (76)	41% (80)	18.5% (36)	45.6% (85)
Work setting	**Acute Hospital (n=132)**	48.5%(64)	31.8% (42)	37.9% (50)	38.6% (51)	22% (29)	51.5% (68)
	Rehabilitation (n=22)	68.2%(15)	36.4% (8)	31.8% (7)	40.9% (9)	9.1 (2)	45.5% (10)
	Community care (n=31)	71% (22)	38.7% (12)	51.6% (16)	48.4% (15)	12.9% (4)	22.6% (7)
Country	**Republic Of Ireland (n=61)**	65.6%(40)	36.1% (22)	37.7% (23)	42.6% (26)	16.4% (10)	37.7% (23)
	United Kingdom (n=49)	46.9%(23)	30.6% (15)	51% (25)	40.8% (20)	22.4% (11)	42.9% (21)
	United States of America (n=58)	43.1%(25)	39.7% (23)	31% (18)	32.8% (19)	19% (11)	65.5% (38)

[22] 195/224 respondents reported experiencing challenges in UOS evaluation. Note respondents could select more than one challenge, which explains the number of challenges selected.

Table 4.17 Availability and Certified Training in UOS Evaluations

	Total	Work Settings (n=210) ***			Countries (n=194) ***			Dysphagia Caseload (n=224)		Clinical Experience (n=224)		Client Group (n=224)	
	n=224	Acute n=147	Rehab n=23	Community n=40	USA n=69	UK n=63	ROI n=62	059% n=78	60-100% n=146	1-10 yrs n=109	>11 yrs n=115	Adults n=170	Paeds/both n=54
a. Availability of UOS Evaluations													
VFS	78.9% (176)	92.5% (136)	82.6% (19)	27.5% (11)	97.1% (66)	81% (51)	59.7% (37)	62.8% (49)	87% (127)	57% (71)	65.2% (75)	82.9% (141)	64.8% (35)
FEES	48.1% (102)	62.6% (87)	26.1% (6)	2.6% (1)	65.2% (43)	47.6% (30)	27.3% (15)	35.9% (28)	50.7% (74)	23.1% (25)	38.3% (44)	52.8% (85)	31.5% (17)
PM	13.9% (28)	18% (23)	4.5% (1)	0% (0)	25.4% (16)	8.9% (5)	9.4% (5)	9% (7)	14.4% (21)	2.8% (3)	5.2% (6)	15.3% (23)	9.3% (5)
Needle EMG*	5.7% (11)	7.4% (9)	4.5% (1)	0% (0)	13.6% (8)	1.9% (1)	0% (0)	5.1% (4)	4.8% (7)	1.9% (2)	16.5% (19)	6.2% (9)	3.7% (2)
b. Certified Training in UOS Evaluations**													
VFS	65.6% (147)	72.7%(109)	50% (12)	39.5% (17)	75.4% (52)	56.7% (38)	68.8% (44)	59% (46)	69.2% (101)	65.7% (71)	65.2% (75)	67.6% (117)	55.5% (30)
FEES	34.5% (69)	41.9% (54)	31.8% (7)	5.1% (2)	54.7% (35)	29.3% (17)	18.2% (10)	33.3% (26)	29.5% (43)	23.1% (25)	38.3% (44)	37.1% (59)	18.5% (10)
PM	5.1% (9)	6.4% (7)	0% (0)	0% (0)	6.9% (5)	0% (0)	4.4% (2)	2.6% (2)	4.8% (7)	2.8% (3)	5.2% (6)	6.6% (9)	0% (0)

(*note training in nEMG not surveyed as not applicable to SLT profession)

(**certified training is defined as attendance at a postgraduate accredited training workshop or course)

*** While there were 224 respondents in survey, sub-group analyses were performed to examine data by country and by work setting. This was completed by selecting the three most common work settings and countries. For this reason, data numbers by country (n=194) and by work setting (n=210) are different to the overall respondent number (n=224).

The second challenge most frequently selected by SLTs was the lack of quantitative information derived from current UOS evaluations (45.6%, 89/195). This was the most commonly reported challenge for SLTs working in acute hospital settings (51.5%, 68/132) and for SLTs working in USA (65.5%; 38/58) (Table 4.16). It was more evident in SLTs working with adults (48.7%, 74/152), in respondents with larger (60-100%) dysphagia caseloads (50.4%, 65/129) and by SLTs with more (>11 years) clinical experience (57.6%, 57/99).

Forty one percent (80/195) of SLTs reported lack of training as a challenge in UOS evaluation. This issue was most apparent in SLTs based in community care (48.4%, 15/31) and those working in ROI (42.6%, 26/61) (Table 4.16). Certified training (i.e., attendance at an accredited training workshop or course) received by SLTs in instrumental examinations (i.e., VFS, FEES and PM) is detailed in Table 4.17. Of concern, certified training in VFS, FEES and PM is distinctly lower across all countries and across all work settings than levels of availability for each of these evaluations. One exception is VFS training in ROI (68.8%, 44/55), which is higher than VFS availability (59.7%, 37/62). This data suggests that SLTs are carrying out instrumental examinations without appropriate training (Table 4.17).

Over a third (39%, 76/195) of SLTs reported lack of knowledge to be a challenge in UOS evaluation. SLTs frequently reported limited focus on UOS opening as part of basic dysphagia training. Lack of knowledge regarding UOS function was particularly evident from SLTs in community care settings (51.6%, 16/31). Of note, lack of knowledge was the most common challenge reported by SLTs working in the UK (51%, 25/49). Lack of knowledge was reported by 50% (7/14) of SLTs with paediatric/mixed caseloads and by 47.4% (45/99) of SLTs with less (1-10 years) clinical experience.

Lack of MDT involvement in UOS investigation was reported as a challenge by over one third of respondents (34.4%, 67/195). This issue was most apparent in community care settings (38.7%, 12/31), and was also frequently reported by SLTs working in USA (39.7%, 23/58) (Table 4.16).

Lack of reliability was selected as a challenge in evaluating UOS dysfunction by less than one fifth of respondents (18.5%, 36/195) (Table 4.16). However, 22% of those working in acute care consider lack of reliability to be an issue with current UOS evaluation. Reliability was also a bigger issue for SLTs with large (60-100%) dysphagia caseloads (21.7%, 28/129) and for those with more (>11 years) clinical experience (20%, 20/99).

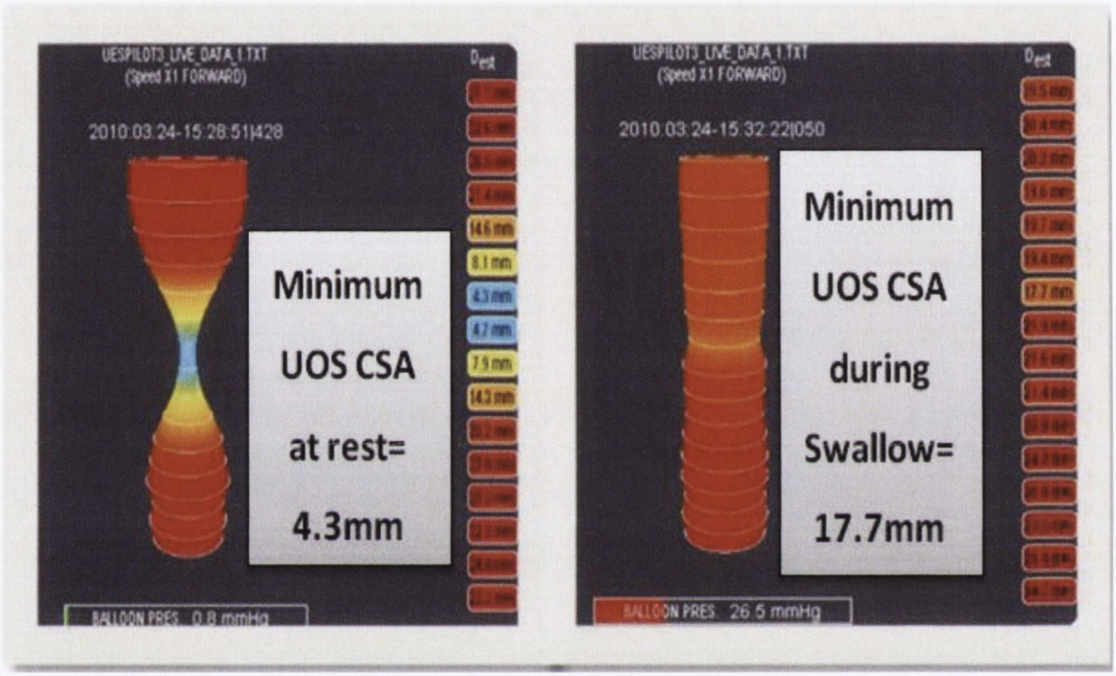

Figure 4.36 Visual Image of EndoFLIP® Data included in Survey

4.4.2.3. Feedback on Potential Role of EndoFLIP® in UOS Evaluation

Based on limited information (including image in Figure 4.36) provided to respondents on the EndoFLIP® evaluation tool within the survey, SLTs were asked how the data provided by EndoFLIP® would be of value to dysphagia assessment and management. The most frequent response was its benefit in detecting usefulness of compensatory strategies (68%, n=151/222) (Figure 4.37). This response was consistent across SLTs with varying levels of clinical experience (67.3-68.4%), across work settings (60.9-74.4%), across countries (66.7-72.6%) and across SLTs with different sizes of dysphagia caseloads (66.2-68.9%). Use of EndoFLIP® to ascertain benefit from compensatory strategies was considered of value more frequently by

SLTs working with adult client groups (72%, 121/168) compared to SLTs with paediatric or mixed caseloads (55.5%, 30/54).

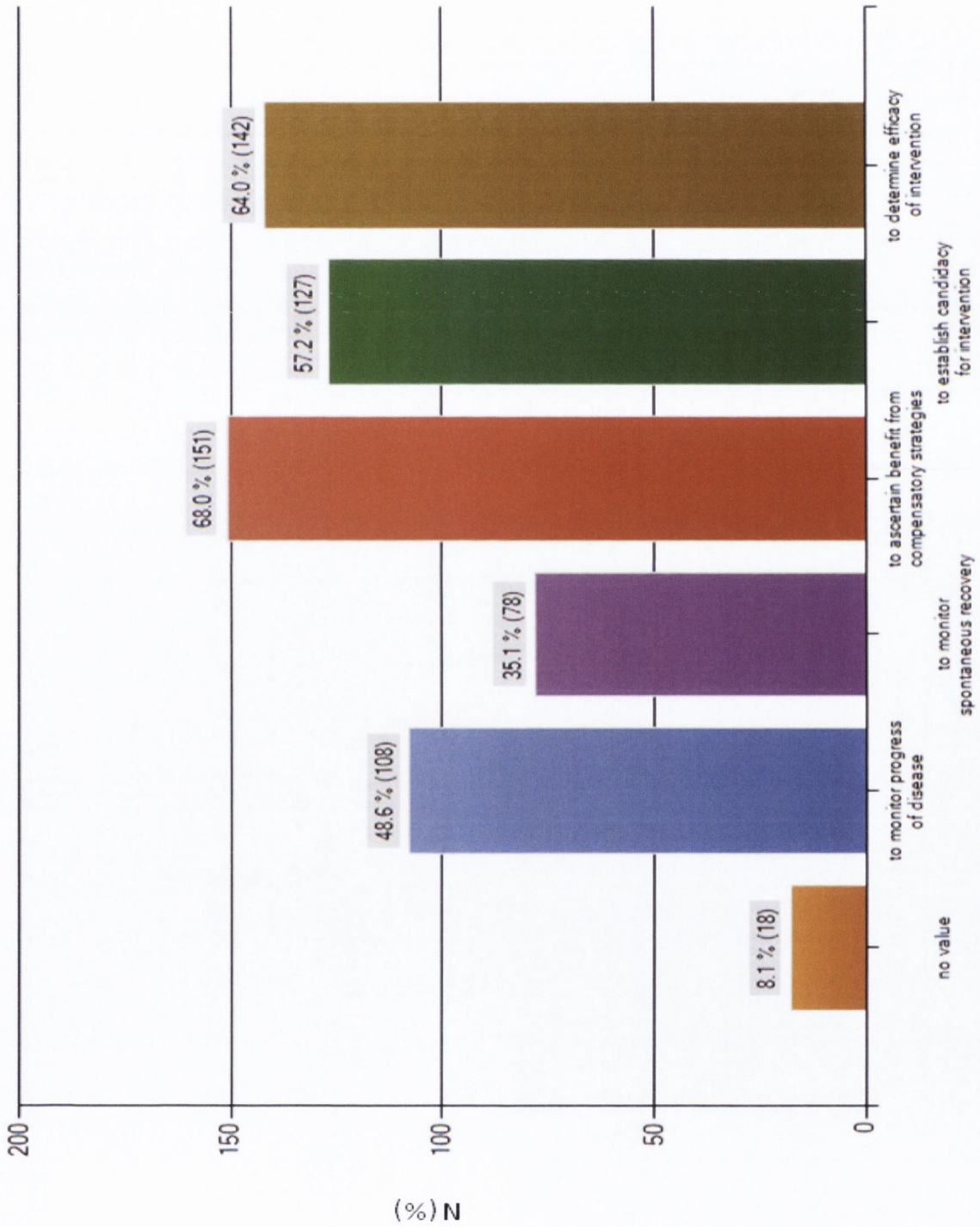

Figure 4.37 Aspects of EndoFLIP® deemed Useful in Dysphagia Practice

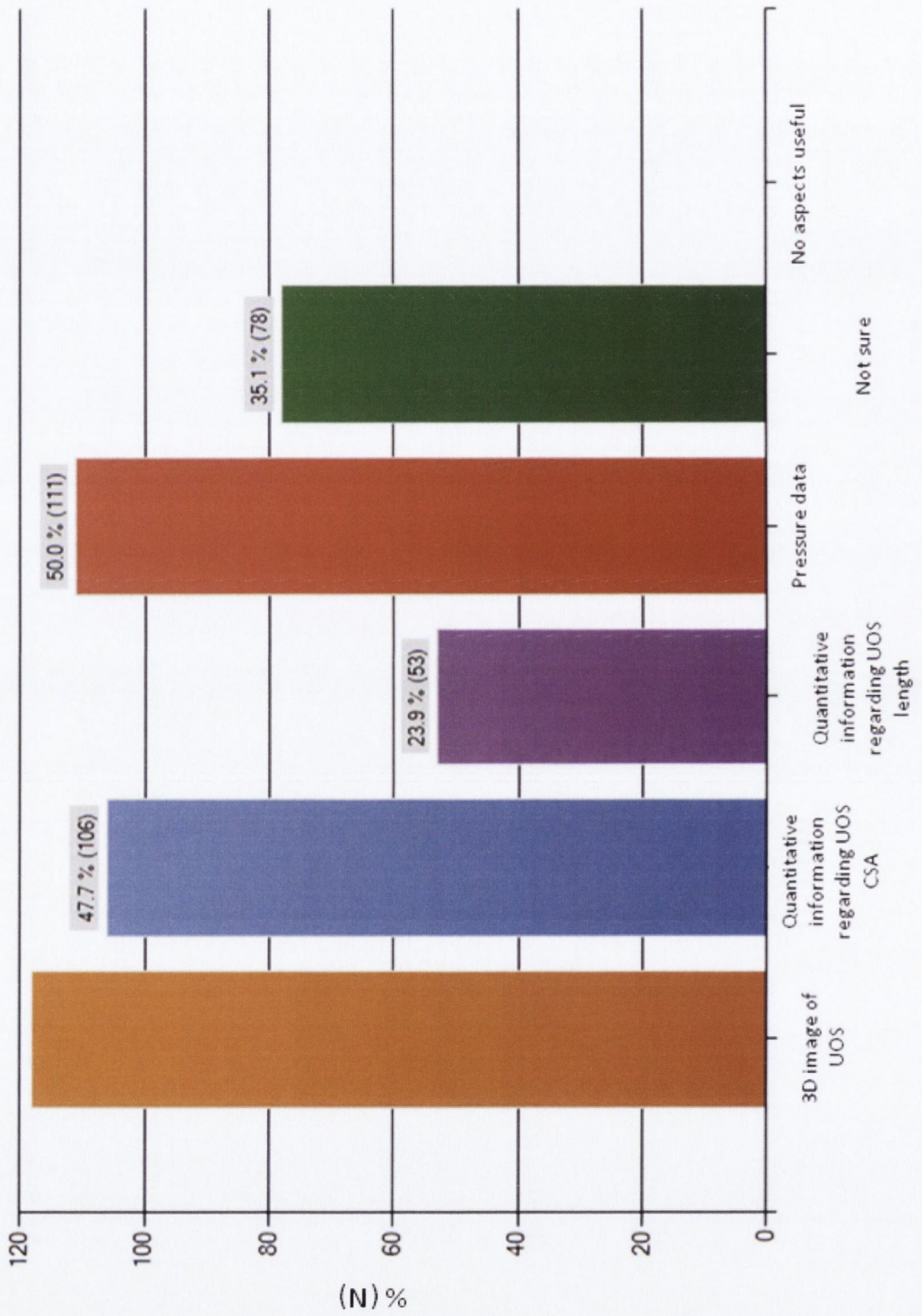

Figure 4.38 Data from EndoFLIP® deemed useful in Dysphagia Practice

When asked what specific data derived from EndoFLIP® would be most useful in management of dysphagia, 53.2% (n=118/221) of SLTs selected the 3D image of UOS (Figure 4.38). Quantitative data regarding UOS CSA was also considered valuable (47.5%, 106/221). Fifty percent (110/221) considered the pressure data derived from EndoFLIP® to be useful to dysphagia practice. Response ranges were consistent across work settings, countries, caseloads and clinical experience.

This chapter has presented results of this research according to the four key research questions posed in Chapter 2.6. In the next chapter, these results will be discussed in the context of previous research.

CHAPTER 5. DISCUSSION AND FUTURE DIRECTIONS

5.0. INTRODUCTION TO DISCUSSION

In this study, research was completed to establish the role of EndoFLIP®, a novel measurement tool, in UOS evaluation. In this final chapter, major findings of the research studies are presented according to the four key research questions initially presented in Chapter 2.6. Results from the separate research studies reported in the previous chapter are discussed in detail, placing them in context of current literature in the area. Key methodological issues and directions for future research are reviewed. The current status of EndoFLIP® as a clinical tool to diagnose dysphagia is debated. Finally, conclusions to this thesis are made based on research conducted to date.

5.1. Research Question 1: Accuracy of EndoFLIP® measures and safe positioning of EndoFLIP® in the UOS in people with dysphagia and in healthy adults

Results from three sub-questions within this first key research question are discussed below.

5.1.1. The effect of transducer position within the lumen of the balloon and balloon constriction on accuracy of EndoFLIP® diameter measurements

Potential sources of error associated with EndoFLIP® diameter measurements in the UOS were introduced in Chapter 2.1.6. Accuracy tests were designed to examine if these sources of error would alter EndoFLIP® diameter measurements within the UOS. Findings indicate that sources of error such as sudden change in wall diameter and deviation of the catheter from the central longitudinal axis are unlikely to alter the accuracy of EndoFLIP® UOS measurements. In other words, the slit like configuration of the UOS and the length of its high pressure zone are unlikely to alter diameter measures obtained. As a result, EndoFLIP® UOS measures obtained from individuals with dysphagia and healthy adults can be assumed to be accurate.

Bench-top experiments conducted to address potential sources of error in this research have demonstrated that EndoFLIP® is an adequately accurate measuring tool for determining the geometry of sphincteric regions under controlled distension. The diameter measurements obtained by EndoFLIP® whilst under varying constraints and whilst manipulated through sharp angles remained adequately accurate as per the operational definition applied in this study (i.e., a maximum percentage difference of 5% between EndoFLIP® diameter measures across conditions).

The transducer position test results presented in Chapter 4.1.1 indicate that the EndoFLIP® probe can accurately measure estimated diameters represented as the cavity diameters in the measurement block (Figures 4.1-4.4). This accuracy remains when the probe is flexed to an angle of 45°, particularly at the higher pressure (i.e., 30mmHg). A trend in the data suggests that the difference between the measured diameter and the actual measure gets smaller as pressure increases within the EndoFLIP® balloon.

In viewing the plots in Figures 4.1 to 4.4, the profiles initially appear to have an almost random shape which, at first, seem to demonstrate a large difference in the diameter measurements across the sixteen electrode pairs. However, within each plot, the range on the y-axis was magnified in order to view more clearly the variance in diameter measurements between electrode pairs, hence giving the random appearance. One might expect that for each profile there would be an almost uniform straight line across the plot, indicating that the electrode pairs all measure the same diameter as each cylinder was machined to be of uniform diameter. In reality this is not the case as there are minor variations at different points throughout the balloon due to the presence of folds, which will be more pronounced at lower balloon volumes. As the IBP increases, these folds are effectively ironed out and the balloon can touch the wall of the cavity, increasing the accuracy of the diameter measurements. Also, minor temperature differences can account for differences in measurements between adjacent electrode pairs.

Balloon constriction test results (Figures 4.5-4.8) indicate that as the thickness (i.e., length) of the washers increased, the EndoFLIP® diameter measurements became closer to the actual diameter value (i.e., accuracy and precision improved as the sharpness of the constriction decreased). Generally, as the volume inside the balloon increased, the diameter values increased even though at a 25ml balloon volume there were no gaps which indicate that the measured data was very close to the mean and that the probe has high precision. This finding indicates that the position of the catheter within the lumen of the balloon has very little (if any) effect on EndoFLIP® diameter measurements. As the angle of the probe changed from 0° to 45° over the prescribed time period, there is very little change in the measured minimum diameter. For each washer size, the measured diameter by EndoFLIP® remained almost constant as the angle changed from 0° to 45° which could mean that the angle of the catheter has little effect (if any) on the diameter measurements.

Potential sources of error such as slope of wall and deviation of the catheter from the central longitudinal axis have been addressed. Research has adequately addressed the effects of radial asymmetry on impedance planimetry and, to a lesser extent, EndoFLIP® measurements (17, 36). These accuracy tests related to the overall curvature of the EndoFLIP® probe balloon and the narrow zones that the probe may be asked to measure indicate that, while it is clear there are variations in the measured values as a result of these challenges, the system remains adequately accurate. This works suggests that EndoFLIP® is suitable to accurately measure narrow regions and curved regions as found in the UOS region and that, technically, the EndoFLIP® probes are suitable for the next stages of the experiments.

These experiments give some indication that the EndoFLIP® probe will provide adequately accurate data for measurements in the region of the UOS. However they do not fully consider issues related to the catheter position within the lumen of the bag. In a cylindrical lumen we can be assured that the catheter will run down the centre of the bag but in a more oval shape lumen which also runs at a curved angle it is highly likely that

the catheter will not run down the centre of the bag. To study the effects of the catheter moving towards and up against the balloon wall a clear tube may be useful where the probe could be bent and the changes across all sixteen CSA measurements could be observed. This type of more elaborate measurement study could be carried out in future technical research into the use of EndoFLIP® but probably falls beyond the remit of this clinical application study.

5.1.2. Safe insertion and positioning of EndoFLIP® into the UOS in people with dysphagia

Based on the 2-5cm length of the UOS reported in the literature review and balloon dimensions within previous UOS research studies, a balloon of 10cm in length with a 2.5cm diameter upon maximum distension was selected for UOS evaluation. This was the original EndoFLIP® balloon designed for OGJ evaluation. This balloon was positioned and safely distended in the UOS under VFS without any airway impingement and it allowed the narrow region of the UOS to be viewed on the EndoFLIP® screen at numerous balloon volumes. The balloon remained in position in the UOS while subjects with oro-pharyngeal dysphagia elicited swallows and subjects could complete postural strategies (e.g., head turn) with the distended balloon in the UOS region. Preliminary quantitative measures of UOS distensibility and opening patterns during swallowing could also be obtained using this balloon design. This balloon was consequently selected for further investigations.

These preliminary studies suggest that EndoFLIP® can be inserted and safely distended in the UOS and can provide useful quantitative data regarding duration and extent of UOS opening. The balloon could be inflated to a maximum of 35mls when positioned in the UOS region. Measures of estimated UOS diameter and IBP could be obtained at rest and during provocative manoeuvres. The researcher observed, however, that IBP levels were increased at rest when the balloon was distended to this volume (i.e., 50-60mmHg). The narrow region of the UOS could be observed from 10ml balloon volume.

Based on these initial studies, the researcher considered trans-oral insertion of the EndoFLIP® balloon to ensure the inflated balloon could be rapidly removed during evaluations, where necessary. This cannot be completed in cases where the probe has been inserted trans-nasally, as investigators must wait until the balloon has been fully deflated before retracting the balloon via the nares. Distensions to 20ml balloon volume were deemed to be most appropriate as the narrow region of the UOS region could be very easily identified on the EndoFLIP® screen and IBP levels were reduced at rest (i.e., 15-25mmHg). Additionally, based on the fact patients could elicit dry swallows with the balloon in position, the researcher considered the introduction of a liquid bolus during future study protocols.

5.1.3. Safe insertion and positioning of EndoFLIP® into the UOS in healthy adults without videofluoroscopic guidance

This final preliminary study tested the use of EndoFLIP® to evaluate UOS dynamics in a pilot group of five healthy subjects. Pilot studies were completed on five healthy subjects, during which the EndoFLIP® probe was inserted trans-orally without VFS guidance. The EndoFLIP® balloon was positioned and distended in the UOS without fluoroscopic guidance and studies were completed without incident or serious adverse event. While all subjects tolerated EndoFLIP® placement in the UOS region, one of five subjects could not tolerate the inflated balloon in the UOS for prolonged periods to complete the study protocol. Further studies will establish tolerance levels.

During distensibility testing, ramp distensions were conducted to a lower maximum volume (20ml) than OGJ studies to ensure the airway was not impinged. Nevertheless, the hourglass shape of the UOS could be observed across subjects at this balloon volume (Figures 4.12 & 4.14) and mean IBP and UOS CSA increased during distension testing (Table 4.2). Maximum UOS diameters during dry and liquid swallowing as measured by EndoFLIP® are similar to VFS measures (77). During swallow event testing, a small

number of subjects did not tolerate 15ml balloon volumes and hence this volume was reduced to 12ml which was better tolerated and yet allowed quantitative measures of UOS opening to be obtained. As subjects tolerated 5ml liquid bolus volumes in this study, the inclusion of a 10ml bolus in future studies would allow the effect of bolus volume to be evaluated.

Based on these pilot studies, a study protocol for UOS evaluation using EndoFLIP® was developed. This protocol consisted of two 20ml ramp distensions (to cater for a habituation effect) and a series of dry, 5ml and 10ml liquid swallows at a 12ml balloon volume to measure UOS opening patterns during swallowing events. Outcome measures for swallow events were defined and included extent of UOS opening (mm), duration of UOS opening (secs) and minimum IBP (mmHg) during swallowing.

5.2. Research Question 2: Normative data on UOS distensibility and UOS opening during swallowing in an adult healthy group using EndoFLIP®

Results on UOS distensibility, UOS opening during swallowing, gender differences in UOS distensibility and UOS opening patterns during swallowing and the effect of postures and manoeuvres on UOS opening during swallowing are discussed below.

5.2.1. UOS distensibility in an adult healthy group using EndoFLIP®

In this study, EndoFLIP® was employed for the first time to evaluate distensibility in a group of fourteen non-elderly (20-50 years) adult healthy subjects. The EndoFLIP® evaluation was well tolerated within the UOS in this subject group (thirteen of fourteen subjects) and the narrow region of the UOS was identified across all subjects on the EndoFLIP® screen during the 20ml ramp distension.

A statistically significant alteration in UOS CSA ($p<.001$) and IBP ($p<.001$) was detected during distensibility testing. During the 20ml ramp distension,

there was a statistically significant increase in UOS CSA between 1ml and 5ml ($p=0.028$) and from 5ml to 10ml ($p<.001$) balloon volumes, from which point the UOS resisted further distension. This resistance was presumably due to the high resting UOS tone within this healthy and non-elderly subject group. From the point where UOS CSA stopped increasing, there was a statistically significant increase in IBP. IBP increased from 10ml to 15ml ($p=0.004$) and from 15ml to 20ml balloon volumes ($p=0.003$). This indicated healthy tone in the UOS.

Care was taken when designing this study protocol to ensure distensibility data was acquired in an accurate and safe manner. Firstly, ramp distensions were chosen to evaluate UOS distensibility as they can be completed in a time-efficient manner (see Chapter 2.1.4). Unlike previous OGJ studies, ramp distensions were completed to a maximum balloon volume of 20mls in order to avoid any airway compromise. To cater for any effect of anxiety on UOS compliance, data from the second ramp distension was analysed. Finally, subjects were advised not to speak or swallow during ramp distensions.

This was the first study to analyse compliance of the UOS lumen using EndoFLIP® in healthy adults. EndoFLIP® measurement of UOS dynamics may contribute to our understanding of UOS function and dysfunction and may, in the longer term, enhance diagnosis and hence the rehabilitative or surgical treatment of dysphagia. It may also help to establish clear candidacy criteria for certain interventions. To date, no other studies have used EndoFLIP® to evaluate UOS distensibility.

5.2.2. UOS opening during swallowing in an adult healthy group using EndoFLIP® and creation of colour contour plots of swallowing

In the same healthy subject group (n=14), extent and duration of UOS opening and minimum IBP during swallowing were evaluated using EndoFLIP®. These measures are currently difficult to reliably quantify in clinical dysphagia practice using VFS and PM (251). EndoFLIP® provided

quantitative measures of the extent and duration of UOS opening and IBP changes over time during dry and liquid swallowing events without any need for radiation.

Duration of UOS opening was 0.5 seconds across dry, 5ml and 10ml liquid bolus volumes in this study ($p=0.91$). Measures of duration of UOS opening closely matched duration measures in previous VFS research (1, 78, 81) (see Figure 5.1). Extent of UOS opening was quantitatively measured using EndoFLIP® across dry (9.6mm), 5ml (8.61mm) and 10ml liquid swallows (8.27mm). VFS studies have found extent of UOS opening in healthy adults to range between 8-12.6mm during swallowing (1, 77, 78, 81) (see Figure 5.2). There was a statistically significant drop in minimum IBP from a baseline of 18.8mmHg during dry (3.6mmHg), 5ml (4.8mmHg) and 10ml liquid swallows (2.96mmHg).

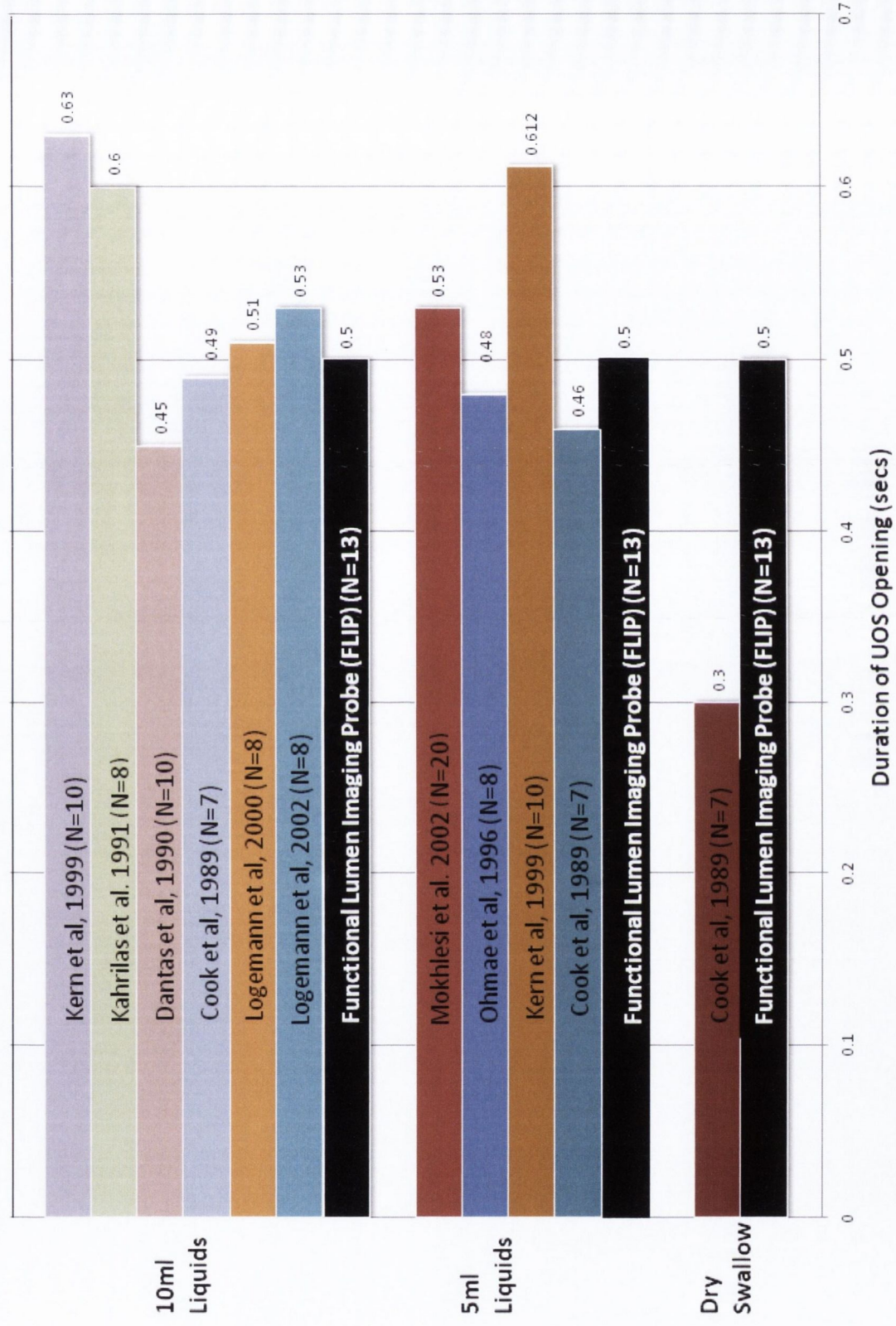

Figure 5.1 EndoFLIP® Measures of Duration of UOS Opening in Healthy Adults Compared to Previous Videofluoroscopy Findings

Figure 5.2 EndoFLIP® Measures of Extent of UOS Opening in Healthy Adults Compared to Previous Videofluoroscopy Findings

While EndoFLIP® measures of UOS opening were similar to VFS, acquisition of EndoFLIP® data is not labour intensive and geometric changes in the UOS during swallowing can be observed in real time on the EndoFLIP® device as a biofeedback tool without any need for radiation. Also, EndoFLIP® is a less expensive, portable tool which can be used at the bedside for those individuals who cannot be transported to Radiology. Another benefit to EndoFLIP® analysis is that barium does not need to be added to the bolus being swallowed, which can increase bolus consistency and hence alter UOS opening findings in VFS studies. Finally, only one combined manofluoroscopy study was found which measured UOS opening during dry swallowing (perhaps due to the lack of barium contrast in the UOS region during VFS). In contrast, duration and extent of UOS opening during dry swallowing can easily be examined using EndoFLIP®.

In this study, extent of UOS opening was largest for dry swallowing compared to 5 and 10ml liquid swallows. The observation of increased UOS opening during dry swallowing may be due to a number of factors. It is plausible that, due to the presence of the balloon in the UOS, subjects needed increased effort to initiate dry swallows, which in turn lead to increased UOS diameter measurements during swallowing. Also, perhaps dry swallows cannot be considered such during EndoFLIP® evaluation, as a distended balloon is positioned in the UOS. The distended EndoFLIP® balloon may simulate a bolus and hence measurements being made during "dry swallows" may differ from VFS studies for good reason. Also worthy of consideration at this point is that swallow volumes and manoeuvres were not randomised during this study protocol, which could have led to some form of an order effect. All subjects completed dry swallows before 5ml and 10ml liquid swallows in head neutral position (see protocol in Figure 3.9). Perhaps, as subjects become more accustomed to the probe in situ, they swallowed with less effort which led to reduced UOS opening measurements during 5ml and 10ml liquid volumes. Minimum IBP during swallowing did not decrease with increased bolus volume (i.e., 10ml liquid) and duration of UOS opening remained the same across dry, 5ml and 10ml liquid swallows. This lack of volume effect has also been reported in VFS and PM studies (198, 252).

The effect of bolus volume on UOS opening during swallowing has been inconsistent across previous VFS studies. Many studies have found that UOS diameter increases with larger bolus volumes (81, 82, 253). In contrast, other VFS research has found no bolus volume effect on extent and duration of UOS opening (198). Importantly, dry swallows were not included in the vast majority of these studies, with bolus volumes being studies ranging from 1ml to 20ml volumes. Where attempts have been made to evaluate UOS opening during dry swallowing in VFS studies, authors reported that onset and offset of UOS opening was not discernible without barium contrast (203). Just one manofluoroscopy study was found which measured UOS opening during dry swallowing (44). The exclusion of dry swallows from previous studies may be due to difficulty measuring UOS opening during VFS without barium contrast in the UOS region. As so few studies have examined UOS opening during dry swallowing to date, these findings will need to be further investigated in future research.

EndoFLIP® data was used to create colour contour plots to visualise UOS opening patterns during swallowing (Figure 4.20 & Figure 4.21). When diameter, pressure and time data provided by EndoFLIP® is depicted in colour contour plots, professionals are provided with an innovative graphic display of the extent and duration of UOS opening on a time axis during swallowing. As detection electrodes within the probe balloon are spaced only 5mm apart, EndoFLIP® can provide a rich profile of UOS dynamics during swallowing and can represent the relationship between UOS opening and IBP. Patterns regarding the sequence and duration of diameter and pressure changes were apparent across swallows in this healthy subject group and may, based on future studies, define whether bolus transport through the UOS is normal or impaired.

Pharyngo-oesophageal swallowing events observed in EndoFLIP® colour contour plots do present similarly to spatio-temporal pressure events on HRM (242) (Figure 2.18). The important distinction, however, is that EndoFLIP® measures changes in the narrowing of a lumen during swallowing, whereas HRM measures of UOS opening are based on pressure changes during swallowing. It is anticipated that the development of new

physiological gastrointestinal tests such as MII, HRM and EndoFLIP® may lead to better diagnostic precision and hence tailor clinical dysphagia intervention. The use of a balloon to study UOS dynamics avoids the issue of pressure sensor displacement from the UOS during swallowing as seen in traditional PM.

This study presented a novel non-radiological technique to quantify extent and duration of UOS opening during swallowing events. EndoFLIP® was well tolerated by subjects and it provided new quantitative measures of UOS opening during swallowing events which are currently lacking in clinical practice. Colour contour plots representing EndoFLIP® diameter and pressure data on a time axis provide a novel objective approach to the analysis of UOS dynamics during swallowing. EndoFLIP® may provide a role in evaluating UOS opening during swallowing in patients with dysphagia before and after rehabilitation or surgery.

5.2.3. Gender differences in UOS distensibility and UOS opening during swallowing in an adult healthy group

A gender difference in UOS distensibility as measured by EndoFLIP® was identified in this study. During distensibility testing, UOS CSA was slightly higher in females at both 1 and 5ml balloon volumes ($p=0.004$ and 0.005 respectively). This may suggest that UOS tone was slightly lower in females (43). Males presented with significantly higher IBP at 5, 10ml and 15ml balloon volumes which, again, may reflect a larger UOS region in males.

A gender difference in UOS opening during swallowing was also identified using EndoFLIP®. UOS diameter was significantly larger in females (9.85mm) than in males (9.46mm) during dry swallows ($p=0.043$), whereas a significantly larger drop in IBP was observed in males than in females during 5ml (3.36mmHg and 7.08mmHg; $p=0.043$) and 10ml liquid swallows (2.64mmHg and 6.22mmHg; $p=0.043$). Duration of UOS opening did not differ across genders, whereas duration of UOS opening has been found to be longer in females in previous research (75, 80) (Chapter 2.2.6). These gender differences need to be investigated further in future research.

5.2.4. EndoFLIP® evaluation of postures and manoeuvres to improve UOS opening during swallowing in an adult healthy group

This study demonstrated for the first time that EndoFLIP® can provide quantitative measures of the extent and duration of UOS opening during swallowing across bolus volumes and during voluntary postural strategies and manoeuvres commonly employed in dysphagia practice. To date, the evidence base for these interventions is limited (Chapter 2.4). This may be due to the fact the effects of voluntary postures and manoeuvres on UOS opening have been measured by VFS and PM, both of which present with major limitations (see Chapter 2.5). Subjects tolerated the EndoFLIP® study protocol and quantitative diameter, pressure and time measures were obtained from EndoFLIP® during swallowing events.

Voluntary postures and manoeuvres significantly affected extent ($p=0.0126$) and duration of UOS opening ($p=0.0013$) and minimum IBP during swallowing ($p=0.0049$), according to EndoFLIP® measures ($n=11$). Compared to the subjective measures obtained using frame by frame analysis from VFS, these objective findings are easy to obtain from a portable non-radiological tool in an outpatient clinic and are potentially very useful to clinical dysphagia practice. As well as identifying these effects from the diameter and pressure data obtained, the alteration in the geometric profile of the UOS on the EndoFLIP® screen during execution of postural strategies and manoeuvres served as useful visual biofeedback for subjects.

Extent of UOS opening (mm) was significantly altered by postures and manoeuvres in this study ($p=0.0126$). However, extent of UOS opening during swallowing was largest in head neutral position (8.62mm) (see Table 4.8 and Figure 4.24). Extent of UOS opening in head neutral position was significantly larger than UOS diameter during head turn right posture (7.54mm) and during supraglottic swallows (7.48mm). A trend towards statistical significance was also found in the mean differences between UOS diameter in head neutral and chin tuck posture. Of note, the chin tuck and

supraglottic swallow were not designed to increase UOS opening (see Chapter 2.4.2). In fact, other research has also found reduced UOS diameter with supraglottic swallows (202). This finding nevertheless highlights the need to objectively verify the indications and effectiveness of these postural strategies and manoeuvres before recommending them in clinical practice. The UOS diameter during the Mendelsohn manoeuvre, which was originally designed to optimise UOS opening during swallowing, was 8.14mm which was slightly below UOS diameter in head neutral position. This finding may be due to improper execution of the strategy by subjects in this study. Consistent accurate completion of the Mendelsohn manoeuvre is certainly a common obstacle in dysphagia practice and accurate performance of the manoeuvre frequently requires substantial training and biofeedback.

Duration of UOS opening was significantly affected by postures and manoeuvres ($p=0.0013$). The Mendelsohn manoeuvre significantly increased duration of UOS opening (by over a tenth of a second) compared to head neutral position (0.46-0.57secs; $p=0.014$). As the Mendelsohn manoeuvre was originally designed to increase and prolong hyo-laryngeal excursion and hence UOS opening (Chapter 2.4.2), this finding is in keeping with the original purpose of this manoeuvre (139). In fact, in a previous VFS study, the Mendelsohn manoeuvre also increased duration of UOS opening from 0.58 to 0.75 seconds on a 10ml liquid bolus in eight healthy volunteers (139). The impact of increased UOS opening on swallow safety and post-swallow residue can be quite significant in clinical practice. Notably, duration of UOS opening was also increased during supraglottic swallowing but this difference was not statistically significant (Table 4.8).

Minimum IBP was also significantly affected by postures and manoeuvres. The drop in minimum IBP during supraglottic swallowing was statistically significant compared to head neutral swallows (4.55--0.13mmHg; $p=0.023$). There was also a marked drop in minimum IBP during swallow with head turn right posture (0.74mmHg) and effortful swallowing (0.53mmHg), although these median changes were not statistically significant. In fact, the chin tuck was the only strategy which did not reduce

the median minimum IBP during swallowing. The researcher proposes that reduced minimum IBP may relate to improved bolus flow.

Several issues present in the interpretation of these findings. Not all postures and manoeuvres examined in this study were designed to increase UOS opening (e.g., chin tuck, supraglottic swallow) and hence an increase in extent and duration of UOS opening was not anticipated across all postures and manoeuvres (see Chapter 2.4.2). Secondly, the beneficial effects of many of these manoeuvres may not be evident in a healthy non-dysphagic population. Perhaps normal subjects swallow most efficiently in head neutral position which may explain, in part, the UOS diameter findings. This issue should be addressed in future studies given the speed of events occurring during swallowing. Another potential limitation to this study, given the number of findings which had a trend towards significance, is that this study may have been underpowered. Future studies with larger subject groups should be completed to ensure this is not the case.

In future studies, the addition of an adjunct measurement (e.g., surface submental EMG) may be of benefit to ensure strategies such as the Mendelsohn manoeuvre and effortful swallow are being executed accurately and consistently. Similarly, validation of the EndoFLIP® measures selected in this study against relatively robust measures from VFS and PM or HRM may help to indicate which parameters are more important to evaluate in clinical practice.

In summary, EndoFLIP® offers a novel non-radiological method to objectively quantify the effects of commonly employed dysphagia interventions on numerous aspects of UOS opening during swallowing which is currently lacking in clinical practice. Based on EndoFLIP® data, findings in this study with regard to the effectiveness of postures and manoeuvres are in keeping with previous research.

5.3. Research Question 3: Comparison of EndoFLIP® measures of UOS opening during swallowing to high resolution manometry with impedance

This study sought to initiate the validation of EndoFLIP® in UOS evaluation. The study compared outcomes from two non-radiological techniques as EndoFLIP® measures of UOS opening were compared to AIM analysis parameters obtained from combined HRM and MII. AIM analysis parameters from combined HRM-MII studies were selected for comparison as the sensitivity and specificity of AIM analysis in detecting aspiration, pharyngeal residue and UOS diameter during swallowing compared to VFS has been established (196, 197, 246) (Chapter 2.5.5.5). Nonetheless, this evaluation tool remains relatively new and is not yet considered a gold standard diagnostic tool. This study was therefore deemed a comparative analysis as opposed to a validation test.

EndoFLIP® measures of UOS opening during swallowing were compared to measures obtained by AIM analysis based on combined HRM-MII studies (n=11). Findings from this study indicate that there was significant interaction effect correlation between EndoFLIP® extent of UOS opening and pressure at nadir impedance (PNadImp) (p=0.034). A significant interaction effect correlation was also identified between EndoFLIP® UOS opening duration and UOS relaxation interval (RI) (p=0.0272). A significant volume dependent effect was observed between EndoFLIP® UOS opening duration and time from nadir impedance to peak pressure (TNadImp-PeakP) (p=0.0269), which was significant on 5ml liquid swallows (p=0.0117).

Interestingly, a statistically significant correlation was not observed between the EndoFLIP® measure of extent of UOS opening (mm) and nadir impedance. This is despite the fact nadir impedance correlated significantly with UOS opening (mm) on VFS in a previous study (246). The lack of correlation in this study may have been due to the presence of the catheter in the UOS in EndoFLIP® studies, or due to the fact examinations weren't acquired simultaneously and hence measures from different swallows were being correlated. However, as outlined previously, VFS measures of UOS

opening are frequently unreliable and hence VFS cannot be deemed a gold standard test of UOS opening.

This study was designed with reference to the QUADAS tool which evaluates the quality of diagnostic accuracy studies (see Chapter 5.5.5) (254). Namely, a minimum delay existed between the performance of tests, with the index test (i.e., EndoFLIP®) and the reference standard diagnostic tool (HRM-MII) being performed on the same day. Also, results from both the index test and reference standard test were blinded. Nonetheless, certain methodological issues should be highlighted before concluding from these results. Firstly, the inability to perform EndoFLIP® and combined HRM-MII simultaneously meant that swallow outcomes being compared were based on different swallows. Given the potential variability between swallows within individuals, the lack of simultaneous examination may have hindered correlation of more parameters. Other factors to consider at this point include the rate of data acquisition across examinations. EndoFLIP® provides ten diameter and intra-balloon pressure measures per second (10Hz), while AIM analysis provided twenty measures per second (20Hz). This different rate of data acquisition may have impacted on findings. This issue will be discussed further in Chapter 5.5.4.2. Other factors which may have limited the number of correlations observed include the lack of range of EndoFLIP® UOS opening duration data and the minimal detectable diameter of 4.8mm by EndoFLIP® due to the width of the EndoFLIP® catheter. Finally, given the number of trends observed within the results (see Table 4.10); the study may have been underpowered with data being acquired from just eleven subjects. This should be addressed in future research.

In this study, UOS opening measures from two non-radiological measurement techniques were compared. EndoFLIP® measures of extent and duration of UOS opening correlated significantly with three AIM analysis measures. This is only a starting point in the validation of EndoFLIP® in UOS evaluation. Future research to establish the diagnostic accuracy of EndoFLIP® is discussed in Chapter 5.5.5.

5.4. Research Question 4: Clinical utility of EndoFLIP® in dysphagia practice

Results from two studies conducted to address this fourth research question are discussed below.

5.4.1. Clinical utility of EndoFLIP® in a population of people with known UOS dysfunction

This was the first study conducted to evaluate UOS distensibility and opening patterns during swallowing in a group with known UOS dysfunction using EndoFLIP®. Initial studies were completed to investigate distensibility of the surgically reconstructed POS and its opening during swallowing in ten patients with total laryngectomy. Individuals with total laryngectomy were chosen for this clinical study due to the isolated structural changes to the UOS (termed POS in this clinical group) in this population (Chapter 2.3.7). In a small cohort of patients with total laryngectomy, a tolerance rate of 70% (7/10) was established for EndoFLIP® evaluation of the POS region. Intolerance of the EndoFLIP® related to a history of UOS stenosis and previous dilatation surgeries. In the seven cases where the EndoFLIP® probe could be passed into the oesophagus, the restructured POS was located on the EndoFLIP® screen during the evaluation across all patients. The geometric profile of the post-surgical POS presented differently to the UOS of healthy controls observed in previous studies. Specifically, the POS was wider and the segment was longer in length.

In this study, distensibility of the POS region was non-radiologically quantified in patients with total laryngectomy using EndoFLIP®. Major findings included; (1) the CSA of the POS region increased significantly throughout the distensibility test ($p<0.001$) and (2) IBP reduced significantly from 1ml to 15ml balloon volume from which point it increased. Distensibility findings from the total laryngectomy group were compared to previously collated UOS distensibility data from healthy controls. There was a statistically significant difference in both CSA and IBP between groups across all (1, 5, 10, 15 and 20ml) balloon volumes during distensibility testing. While CSA plateaued in the healthy control group with good UOS

tone, it continued to increase throughout the ramp distension in the total laryngectomy group. This suggests lower POS tone in the total laryngectomy group, which may relate to myotomy performed during laryngectomy surgery. This lower POS tone may explain the higher incidence of pharyngeal and nasal regurgitation in this clinical group. The different distensibility patterns across the two groups, despite the reduced distension volume in this study protocol, indicates that 20ml ramp distensions may be sufficient to detect differences in UOS distensibility between healthy and disordered groups.

While only a small cohort of patients were studied, these findings indicate that the tone of the POS of patients with total laryngectomy was somewhat reduced. This may be expected given the surgical history of these patients, including resection and reconnection of IPC and CP muscles and the CP myotomy performed during total laryngectomy surgery. Reduced POS tone can contribute to impaired bolus clearance and pharyngeal regurgitation of swallowed material from the oesophagus. These issues are frequently reported in patients with total laryngectomy (99). Given these findings, EndoFLIP® may provide a clinically useful role in the outpatient ENT setting to determine candidacy for or to establish effectiveness of dilatation surgeries, among other interventions, in the POS region in patients with total laryngectomy.

EndoFLIP® also provided quantitative measures of the extent and duration of POS opening during swallowing in adults with total laryngectomy in this study without any need for radiation. A statistically significant change in POS diameter was detected across swallow events ($p=0.002$), with widest POS diameter observed for 10ml liquid swallows (7.65mm). When compared to data from healthy controls, resting POS diameter was wider (5.05mm) than UOS diameter in healthy controls (4.9mm) ($p=0.018$). While statistically insignificant, POS diameter was narrower than UOS opening in healthy controls across dry, 5ml and 10ml liquid volumes. This limited POS opening may be due to altered suprahyoid contraction and absent hyo-laryngeal excursion. These factors may limit the stretching open of the POS region during swallowing. Interestingly, duration of POS opening

was significantly longer in the total laryngectomy group across bolus volumes than duration of UOS opening in healthy controls. This finding may relate to altered POS tone as CP contraction post swallow may be delayed or disordered in the surgical group. The increase in POS opening may be of benefit to total laryngectomy patients as it allows the bolus to clear efficiently during swallowing. However, it may also increase the risk of pharyngeal regurgitation post swallow.

There are a number of issues within this study which should be considered. Firstly, the method of probe insertion differed across total laryngectomy and healthy control groups. The total laryngectomy patients had the probe passed trans-nasally while healthy subjects had trans-oral insertion of the EndoFLIP® probe. While it is suspected that data is unlikely to differ depending on mode of insertion, this should be investigated in future research. The emergence of trans-nasal oesophagoscopy (TNO) in ENT clinics has lead to the delivery of numerous trans-nasal therapeutic procedures, such as balloon dilation of the oesophagus, BoNT-A injections and trachea-oesophageal (TE) punctures (255, 256).

The second methodological issue in this study was the difference in median age across groups, with older subjects in the total laryngectomy group. Age has been proven to impact on UOS opening during swallowing (Chapter 2.2.6). Hence, this factor needs to be taken into account. The effect of age on UOS distensibility and opening patterns as measured by EndoFLIP® needs to be examined in future research (see Chapter 5.5.1.1). However, this was an initial examination of the role of EndoFLIP® in measuring UOS distensibility and opening patterns in a small clinical group. For this reason, recruitment was limited to a small subject group. However, in order to conclude from findings, subjects with wider age ranges should be included in future studies.

Finally, a validated rating scale was not employed during clinical studies to establish tolerance and acceptability of the EndoFLIP® evaluation or to evaluate dysphagia severity across subjects with laryngectomy. The inclusion of a simple visual analogue scale, as used in recent trans-nasal

endoscopy studies, would have established patient tolerance of probe insertion and balloon distension in the UOS (257, 258). Informally, subjects who completed the study protocol reported that the EndoFLIP® evaluation was similar in acceptability to FEES examinations. In terms of dysphagia severity, all subjects recruited informally reported some level of swallowing difficulty. Inclusion of a dysphagia rating scale such as the SWAL-QOL or the EAT-10 would have allowed the researcher to have provisionally investigated a link between EndoFLIP® outcomes and dysphagia severity (259, 260). This should certainly be investigated in future research.

This is the first study conducted to establish the role of EndoFLIP® in UOS evaluation in a clinical population. A seventy-percent tolerance rate was observed in a small cohort with total laryngectomy. EndoFLIP® provided novel information regarding the distensibility of the post-surgical POS region. POS distensibility was increased compared to UOS distensibility in healthy control subjects which suggests reduced tone in this region. EndoFLIP® also provided quantitative measures regarding the extent and duration of POS opening during swallowing in total laryngectomy patients. Extent of POS opening was reduced compared to healthy controls. However, the duration of POS opening was significantly longer. EndoFLIP® provides useful objective data which is currently lacking in clinical practice. This information, which can be easily obtained in an outpatient clinic without need for radiation, may be of considerable benefit in establishing both candidacy for and effectiveness of dysphagia and speech interventions (e.g., dilatation surgery, BoNT-A injections and CP myotomy described in Chapter 2.4) in patients with total laryngectomy. Further research is required to validate its use in UOS evaluation.

5.4.2. Satisfaction of dysphagia clinicians with current UOS evaluation and feedback on the potential role of EndoFLIP® in clinical dysphagia practice

Survey responses from 224 SLTs with active dysphagia caseloads were analysed to obtain feedback regarding UOS evaluation and the potential use of EndoFLIP®. Only 17.9% (40/224) of SLTs are satisfied with the accuracy

and reliability of UOS evaluations currently being employed in dysphagia practice. Satisfaction with current UOS evaluation was not associated with level of clinical experience ($r=0.078$; $p=0.246$). Eighty-seven percent (195/224) of SLTs working with dysphagia experience challenges in UOS evaluation. Challenges reported include lack of resources/equipment (55.9%), limited quantitative information (45.6%), lack of training (41%) and knowledge (39%) in UOS function and limited MDT involvement (34%).

SLTs internationally are dissatisfied with current methods of UOS evaluation and experience multiple challenges in assessing UOS function in people with dysphagia. The low satisfaction levels with current UOS evaluations are evident even in highly specialised clinicians and are a cause for concern. If SLTs are experiencing difficulty diagnosing the presence, severity and cause of impaired UOS opening, people with dysphagia may not be receiving appropriate dysphagia treatment (86). Completion of a similar survey on other health care professionals involved in the management of UOS disorders (e.g., Ear Nose and Throat surgeons) may be of interest to determine if comparable satisfaction levels are found and the same challenges are encountered.

The biggest challenges in current UOS evaluation reported by SLTs relate to resources/equipment. This is despite the fact that access to VFS and FEES was higher in this survey than in previous research (191, 261). Access to equipment was reported as an issue across all countries, but most noticeably in ROI, perhaps due to the late development of dysphagia services in this country, commencing only in the 1990s. Dysphagia services in ROI are also not provided routinely in private medical care settings and rely largely on public sector funding. Interestingly, availability of resources has been reported as a challenge across all work settings, despite variation in equipment availability. In rehabilitation and particularly community care settings, routine access to a "first port of call" instrumental evaluation of swallowing (i.e., VFS or FEES) is limited. This is not surprising given the lack of Radiology or ENT departments in these settings. Perhaps the joint development of a care pathway for referring people for VFS/FEES

examinations in local acute care settings from the community/rehabilitation setting may address, at least in part, this issue.

In acute care and adult services, access to VFS and FEES are much improved but availability of physiological measurements (e.g., PM and EMG) in order to accurately identify the cause of UOS dysfunction is inconsistent. Additionally, where SLTs in acute care and adult services do have access to physiological measurements, lack of quantitative information derived from current UOS evaluations continues to pose a challenge when measuring UOS opening for swallowing. It is hoped that the adaptation of GI evaluations (e.g., HRM, MII) and their combination with VFS will address this issue of reliable quantification in UOS evaluation in the future. The development of a relatively low cost tool with established sensitivity and specificity that is portable and not confined to acute settings would be ideal to address this gap in UOS evaluation.

Based on survey findings, challenges encountered with UOS evaluation in dysphagia practice are not restricted to resources and equipment. An independent challenge frequently reported by SLTs was a lack of knowledge regarding impaired UOS opening. Numerous respondents highlighted a limited focus on normal phases of UOS opening and the various causes of impaired UOS opening as part of basic dysphagia training. SLTs queried whether impaired UOS opening can be caused by a weakness at the pharyngeal stage of swallowing (e.g., reduced hyo-laryngeal excursion). This lack of clarity is confusing SLTs regarding their role in the management of impaired UOS opening. Additionally, respondents report confusion regarding definitions such as "UOS dysfunction", "UOS achalasia" and "UOS spasm", and whether these terms refer to CP relaxation alone or if they encompass the multiple potential causes of impaired UOS opening. Poor awareness of optimal treatment for varying causes of UOS impairment was also described, which has major implications for the patient with dysphagia. Specifically, SLTs were unsure regarding candidacy criteria for rehabilitation versus candidacy for referral to ENT/GI colleagues.

Knowledge gaps pertaining to UOS opening reported by SLTs may also relate to limited certified training (i.e., attendance at a postgraduate accredited training workshop or course) in instrumental assessments used to evaluate the UOS (Table 4.17). A marked disparity exists across all countries and work settings between access to VFS, FEES and PM and certified training to perform and analyse these evaluations (Table 4.17). Compulsory attendance at a certified training course in order to complete and analyse any examinations (e.g., VFS and PM) may address knowledge gaps and improve reliability of interpretation. The third area which presented as a challenge for SLTs across all work settings is lack of routine care pathways in the MDT management for patients with impaired UOS opening (Table 4.16). It is interesting that MDT dysphagia management is an issue which is surfacing across the USA, UK and ROI despite differences in the delivery of healthcare services (Table 4.16). Perhaps ambiguity regarding the roles of various MDT members reflects, in part, the recent growth in the number of MDT interventions being developed and refined to treat dysphagia (164, 172, 187, 262). SLTs report frequent confusion regarding which professional (i.e., ENT/GI surgery) to refer to for further UOS investigation. SLTs describe unheeded requests for UOS investigation and limited interventions for those who are reviewed by ENT/GI colleagues. The need for closer collaboration with ENT/GI colleagues was expressed by many respondents. SLTs also communicated a lack of clarity regarding the extent of their role in UOS investigation within the MDT. SLTs also report that they are unsure how much information they are expected to provide to colleagues when referring patients for further UOS investigation. This uncertainty regarding MDT roles would surely be enough to independently complicate the management of impaired UOS opening in people with dysphagia. Again, the development of explicit care pathways and referral criteria at a local level may address some of these areas of concern.

Based on the basic data provided within the survey, feedback provided by SLTs suggests that EndoFLIP® may, based on future research, serve a useful role in UOS evaluation. Specific roles for EndoFLIP® suggested by SLTs include determining efficacy of compensatory strategies and dysphagia interventions (Figures 4.37 & 4.38). The use of EndoFLIP® to establish

candidacy for intervention was also highlighted by SLTs. This was reported from SLTs across subgroups but was most evident from SLTs working with adults in acute care settings. These proposed roles may relate to the quantitative measures and visual imaging of UOS opening provided by EndoFLIP® which can be viewed while the probe is positioned in the UOS (263). Changes in UOS CSA can therefore be monitored while patients trial various dysphagia strategies (e.g., head turn). This information provided by EndoFLIP® may address to some degree the lack of objective data currently available to demonstrate candidacy for or efficacy of management. It is strongly recognised, however, that in order for these potential roles of EndoFLIP® to be further explored, issues such as validity and reliability will need thorough testing, normative data on young and older healthy volunteers will be required and training requirements will need to be met. Additionally, it was recognised that 8% of respondents viewed EndoFLIP® as being of no value to clinical practice. It may be the case that a similar percentage tends to respond similarly in response to the introduction of a new evaluation tool. Many professionals may not consider a tool until further validation work has been completed. Nonetheless, this is a finding which should be investigated in more detail in future research and re-tested upon completion of more validation work.

In terms of limitations to the survey design, the primary researcher acknowledges that, due to the sampling decisions made within this survey and the nature of questions posed, there may be bias within the data obtained. Instead of describing EndoFLIP® in isolation within the survey, the introduction of several new or fictive methods to respondents might have reduced bias as the researcher could have determined if SLTs would have responded positively to any method. It could also be argued that findings in relation to therapists' concerns about information and resources available to them are not unique to dysphagia evaluation. The need for training has been highlighted within surveys across many areas of clinical practice beyond dysphagia evaluation (264, 265). However, lack of and inconsistenct training practices and limited resources remains a common theme in dysphagia literature (14, 191, 261). Hence, similar findings in other clinical areas should not necessarily invalidate these findings.

This survey investigated issues within the SLT profession with current UOS investigation in people with dysphagia. While responses were largely from highly specialized clinicians, focus on less experienced clinicians and those with smaller dysphagia caseloads were also included. There is great dissatisfaction with current evaluation of UOS opening during swallowing within the SLTs surveyed, which is not limited to less experienced clinicians. Current techniques may not be providing all of the information required by SLTs in order to deliver appropriate dysphagia treatment. Lack of resources/equipment, limited quantitative measurement of the UOS, inadequate knowledge and training and lack of MDT care are all key concerns. In order to progress UOS evaluation within the SLT profession, specific measures need to be taken. These include (1) increased emphasis on normal and abnormal UOS opening as part of basic dysphagia training to increase knowledge base; (2) improved access to and training in standard and newer GI physiological evaluations adapted to objectively evaluate UOS opening; (3) established local MDT care pathways to accurately diagnose and appropriately manage individuals with impaired UOS opening and (4) the development of new diagnostic methods to objectively and reliably measure UOS function. This study provides a starting point for examining this area.

Next, methodological issues based on research to date will be discussed and directions for future research will be outlined.

CHAPTER 5.5. METHODOLOGICAL ISSUES AND DIRECTIONS FOR FUTURE RESEARCH

Several aspects of UOS evaluation using EndoFLIP® require deliberation by the researcher before further testing is completed. Many of these issues (e.g., mode of probe insertion and use of local anaesthesia) are not unique to EndoFLIP® evaluation and are also encountered in PM and FEES evaluations. Nonetheless, each of the aspects encountered throughout this research are addressed below within subject, materials, and study protocol and data analysis categories.

5.5.1. Subjects

5.5.1.1. Normative Data in Healthy Elderly

This research focused on the acquisition of normative data from healthy non-elderly volunteers between the ages of 20-50 years. The researcher chose to initially recruit a non-elderly subject group in order to evaluate healthy UOS function without effects of ageing on the UOS and swallowing physiology. This decision is in keeping with previous research studies in this area and it was considered by the researcher to be an ethically sound decision when the safety of EndoFLIP® probe insertion into the UOS was unknown (203, 253). Nonetheless, it is acknowledged that a considerable proportion of adults with dysphagia would not be captured within this age range, highlighting the need to investigate UOS distensibility and opening patterns in older subject groups in the future.

Numerous research studies have identified the effects of ageing on UOS function (43, 77, 80, 198, 200). Firstly, the length of the UOS high pressure zone has been found to be shorter in elderly groups, perhaps due to a shift in the contribution of varying muscle components to the UOS (43). Resting UOS pressure has been found to be lower in the elderly (43, 67, 266). A reduction in the extent of UOS opening during swallowing has also been found in elderly adults (67, 198, 200). This has been related to an age-related reduction in distensibility of the CP muscle, as evidenced by increased hypo-pharyngeal intra-bolus pressure in response to resistance to

flow in older subjects (67, 266). Anterior hyo-laryngeal excursion, which applies traction forces to the relaxed CP muscle during swallowing, is also reduced in the elderly (198, 200). Causes of reduced UOS opening therefore appear to be multi-factorial in nature (see Figure 2.5). Duration of UOS opening has been found to be increased in the elderly (67, 77, 198). It has been hypothesised that this may be a compensatory strategy for reduced UOS opening to ensure a swallowed bolus can pass safely and efficiently into the oesophagus (198).

Given the high prevalence of dysphagia in elderly and the alterations in UOS function in this group, examination of UOS distensibility and opening patterns during swallowing in healthy elderly volunteers (i.e., ages 60-90) using EndoFLIP® should be an integral part of the normative data acquisition process and needs to be included in future research. Using the same study protocol used in this thesis, findings could be compared to non-elderly healthy subjects to determine the effect of ageing on UOS function.

5.5.1.2. Clinical Data

Once normative data has been adequately established, the researcher plans to undertake in-depth testing of homogeneous clinical groups to identify the effect of disease on UOS opening patterns. Clinical populations with known UOS dysfunction should be considered for UOS evaluation using EndoFLIP® (see Table 2.1). Considerable research has already been conducted investigating the nature of UOS dysfunction in these groups. EndoFLIP® findings can therefore be analysed in the context of previous research.

Evaluation of UOS distensibility in individuals with dysphagia may provide very valuable results. Clinical groups with increased UOS tone and poor bolus transfer during swallowing (e.g., brainstem stroke, inflammatory myopathies and post radiation fibrosis) may demonstrate reduced UOS distensibility. In contrast, those with reduced UOS tone (e.g., myasthenia gravis or Zenker's diverticulum) may exhibit increased distensibility during EndoFLIP® evaluation. These measures may therefore act as a useful outcome measure in dysphagia intervention as EndoFLIP® findings may

determine the efficacy of and candidacy for rehabilitation and surgical interventions described in Chapter 2.4.

Multiple clinical groups have been reported to present with reduced UOS opening during swallowing, leading to various clinical sequelae of dysphagia including weight loss and aspiration pneumonia. Individuals with motor neurone disease have been found to have shortened periods of CP relaxation during swallowing and those with Parkinson's disease have absent CP relaxation before the onset of any swallowing difficulties. This can be indicative of medullary disease. Comparison of EndoFLIP® data to needle EMG into the CP muscle may establish how sensitive and specific EndoFLIP® is in detecting impaired CP relaxation during swallowing. This would be a major finding as currently, CP relaxation can only be detected by needle EMG or by combined manofluoroscopy, neither of which are easily accessible in current clinical practice. Those with disordered CP relaxation may respond better to invasive interventions and EndoFLIP® may serve to detect ideal candidates for these procedures.

Individuals with myasthenia gravis may present with reduced hyo-laryngeal excursion. Individuals with stroke will present variably depending on the site and extent of the lesion, although those with brainstem involvement are more likely to have specific UOS dysfunction. Colour contour plotting of diameter, pressure and time data across these different groups will determine how these different features will present based on EndoFLIP® data. Ideally, those patients already attending for VFS can also be evaluated with EndoFLIP® and findings can be correlated. Also, the role of EndoFLIP® in determining either the recovery or the progression of UOS dysfunction over time should be identified. If EndoFLIP® can accurately monitor any change in UOS function over time; it may reduce the need for repeated VFS.

5.5.1.3. New Clinical Conditions

EndoFLIP® evaluation may also provide useful information regarding the nature of UOS dysfunction in a number of conditions which are less well understood. For example, globus pharyngeus (the sensation of a lump or

discomfort in the throat) is a relatively common complaint reported to ENT and Gastroenterology teams. However, the nature of UOS dysfunction in this diagnostic group cannot be captured on manometric and barostat evaluations, perhaps causing the condition to have been referred to as globus hystericus in the past. Currently, one hypothesis is that this sensation is caused by altered tone in the CP muscle within the UOS. Perhaps EndoFLIP® data may provide valuable information regarding the nature of impairment in this condition and hence contribute to better future management. Equally, researchers frequently debate whether the presence of a CP prominence or bar (a posterior bar or protrusion at the level of the CP muscle during swallowing) on VFS relates to swallow dysfunction or not. CP bar has been related to CP spasm, fibrosis and GORD. A better understanding of UOS dysfunction associated with the presence of CP bar based on EndoFLIP® evaluation may promote improved intervention.

5.5.1.4. Establishing effects of Pharmacological and Surgical Interventions

The varying evidence base for invasive interventions such as BoNT-A injections and CP myotomy based on current diagnostic tools was highlighted in Chapter 2.4. The researcher plans to complete distensibility testing on patients with dysphagia who are due to attend for pharmacological and surgical interventions to improve UOS opening such as BoNT-A injections and CP myotomy procedures. These procedures have a potentially pivotal role in dysphagia management and yet their candidacy criteria and evidence-base is unclear based on videofluoroscopic and manometric data. EndoFLIP® may establish the effect of these interventions in two ways. EndoFLIP® evaluation can be completed before and after BoNT-A injections, CP myotomy, upper oesophageal dilatation or CP myotomy to objectively determine changes in UOS compliance and UOS opening during swallowing. EndoFLIP® findings could be combined with functional outcome measures such as oral intake, weight chest status and quality of life ratings. Secondly, as in fundoplication surgery of the OGJ, EndoFLIP® may serve an inter-operative role during UOS surgery (i.e., to establish if myotomy or dilatation has been sufficient or if further intervention is required).

5.5.2. Materials

5.5.2.1. EndoFLIP® Balloon Design

While the study protocol in this research was adapted from OGJ studies for UOS evaluation, the probe used in these studies is a standard version for use in other regions of the oesophagus. Based on UOS studies conducted by the researcher to date, healthy controls have demonstrated good tolerance (13/14) of the probe insertion and of the distended balloon in the UOS, albeit with smaller balloon volumes. Likewise, all individuals with dysphagia who had the probe successfully inserted into the oesophagus (i.e., two pilot studies under VFS and seven total laryngectomy patients) demonstrated tolerance of the distended balloon in the UOS. Nevertheless, certain changes to the EndoFLIP® balloon design have been identified by the researcher which might optimise future testing.

Studies to date suggest that EndoFLIP® balloon length and positioning need to be carefully considered during future UOS testing. Care had to be taken to ensure that too much of the balloon was not positioned in the pharynx during testing. This was achievable by monitoring the geometric profile of the UOS on the EndoFLIP® screen during procedures. Otherwise, tolerance of the balloon decreased as subjects were very sensitive to the inflated balloon in the pharynx. This intolerance was more pronounced in healthy subjects, presumably due to preserved pharyngeal sensation. While a shorter probe balloon may address this issue to some extent, too short a balloon might prevent the UOS opening from being captured due to its upward shift during swallowing. Refinement of balloon dimensions and positioning during the study protocol is of prime importance to ensure that critical information is not lost during data collection.

Reduction of the catheter width is likely to minimise any discomfort to patients during probe insertion. Use of a balloon which distends to a narrower maximum diameter than 2.5cm may optimise tolerance levels, minimise discomfort and lead to the acquisition of data which has not been confounded by anxiety, altered tone in response to balloon distension or other physiological parameters. A balloon with a narrower width may also

facilitate the elicitation of swallows of larger bolus volumes and thicker bolus consistencies. In vivo studies under VFS would establish if the new balloon design can locate the UOS as clearly as the original balloon and if data derived from a narrower balloon can capture distensibility and opening patterns as efficiently. If experimenting with a narrower balloon volume, alternative maximum balloon volumes for ramp distensions and swallow events would need to be determined.

The development of a balloon design with a narrower detectable minimum diameter (i.e., less than 4.8mm) would increase range of UOS opening measures. Finally, a balloon with a longer measurement area (i.e., more detection electrodes within the balloon) would provide more information regarding UOS opening during swallowing and would reduce instances where UOS measures are lost during swallowing due to its upward shift.

In summary, balloon design changes for future testing should include:

a) Smaller catheter
b) Narrower maximum balloon diameter
c) Smaller minimum diameter
d) Longer measurement area to capture the upward shift of the UOS during swallowing.

In order to investigate the balloon design for UOS evaluation further, a number of prototype balloons have already been designed by the researcher and made on the bench with balloon widths varying from 0.8-2.5cm (Figure 5.3). These balloons can be positioned over the excitation and detection electrodes on the EndoFLIP® probe and sealed on either end in order to contain the conductive solution when distended.

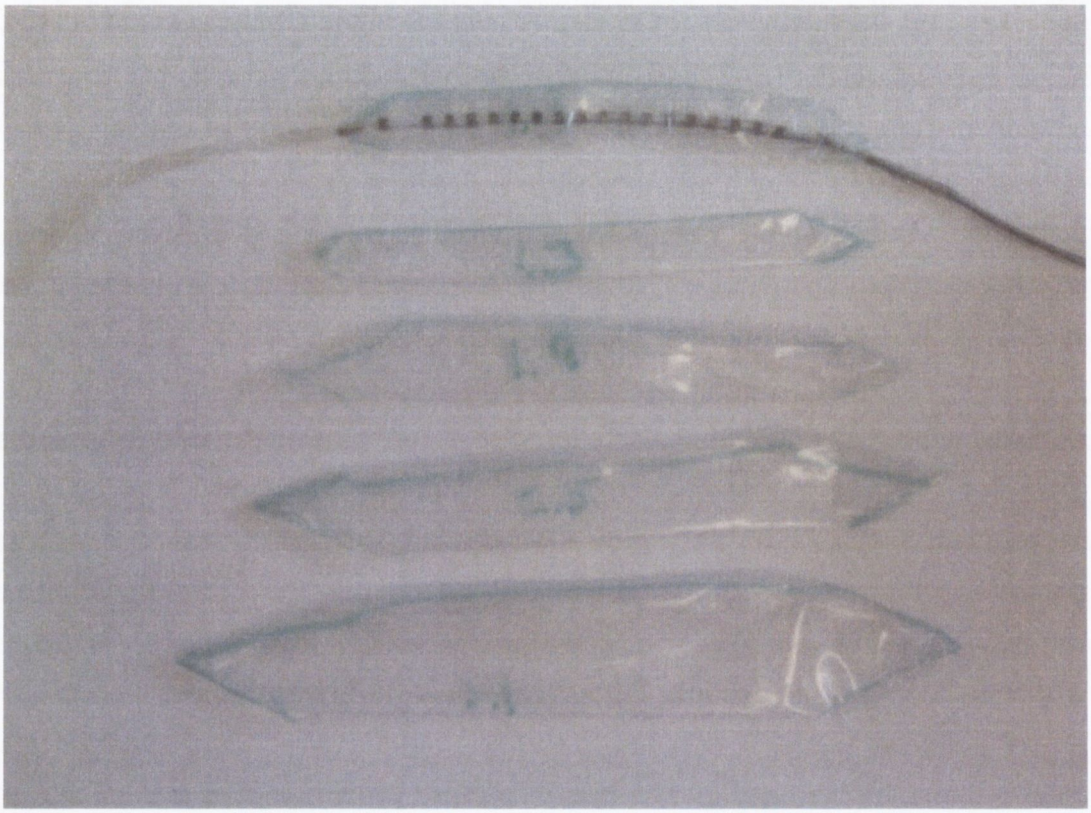

Figure 5.3 Custom made EndoFLIP® Balloons with Varying Diameters for Future UOS Studies

5.5.2.2. Tagging System on EndoFLIP® Device

During the studies described in this thesis, the primary researcher needed to document the timing of swallow events throughout study protocols to direct data analysis (see Appendix 5). This proved to be quite labour intensive as another researcher needed to hold the EndoFLIP® catheter in position and control balloon volumes on the EndoFLIP® screen. When the researcher conducted EndoFLIP® evaluations alone with total laryngectomy patients, the exact time of various swallow events were stated (e.g., "first dry swallow at x time") and evaluations were audio-recorded.

This process could be easily simplified to allow one clinician to more easily complete the evaluation protocol and data analysis. The development of a tagging system on EndoFLIP® would be of great value to the collection and

analysis of EndoFLIP® data. This would ensure that distensibility tests, swallow events or other provocative manoeuvres could be easily marked at execution and easily identified after the examination. This would eliminate the need for two researchers to complete an evaluation and prevent the need to audio-record or document the timing of events during the procedure. Tagging is currently available on digital VFS systems and on HRM systems. It allows for a less labour-intensive procedure and more time-efficient analysis. Alternatively, if audio-recording was available on the EndoFLIP® system, the various aspects of the evaluation protocol could be easily identified during analysis.

5.5.3. Study Protocol

5.5.3.1. Trans-nasal or trans-oral probe insertion of probe

The researcher experimented with both trans-nasal and trans-oral passing of the EndoFLIP® catheter throughout this research (Table 5.1). During pilot studies, the catheter was passed trans-nasally, a method in keeping with FEES and manometric evaluations (Chapter 2.5). This was done to minimise any alteration to the oral phase of swallowing and to avoid spraying local anaesthetic to the posterior pharyngeal wall, which could alter sensory or swallowing function. It was observed during in vivo tests that, in a case where a patient wants the probe to be removed promptly, clinicians must wait until the balloon is deflated before removing the catheter trans-nasally. However, the balloon was being inflated to large volumes (35ml) during pilot studies. In the subsequent study protocol, the maximum inflation was to a 20ml balloon volume, reducing the likelihood of the balloon popping out of the UOS and into the oral cavity.

Table 5.1 Benefits and Limitations to Trans-Nasal or Trans-Oral of EndoFLIP® for UOS Evaluation

	Trans-nasal insertion of EndoFLIP®	**Trans-oral insertion of EndoFLIP®**
+	Anchors EndoFLIP® balloon in position in UOS.	Distended EndoFLIP® balloon can be removed rapidly from UOS region, if required
	Does not interfere with oral phase of swallowing or with the completion of postures and manoeuvres.	
	Less gagging observed.	
	Similar insertion method to FEES and PM or HRM.	
	Local anaesthetic to nares only.	
-	Safety- probe cannot be removed trans-nasally until the balloon has been deflated (unless balloon deflated manually using syringe).	Local anaesthetic is sprayed onto the posterior pharyngeal wall which can alter sensation and swallowing.
	Increased risk of epistaxis (nose bleed) and vasovagal events, although this was not found in FEES research.	Impinges on oral phase of swallowing.
		Can induce gagging.
		Patients with laryngectomy requested trans-nasal insertion.

The EndoFLIP® probe was passed trans-orally in all studies completed in the Neurogastroenterology clinic in Leuven Hospital, Belgium (Chapter 3.3 & 3.4). This was due to the fact healthy volunteers recruited for UOS evaluation using EndoFLIP® were also attending for a UOS barostat study on the same day which involved oral probe insertion and local anaesthetic spray to the posterior pharyngeal wall. Local researchers were also very experienced at oral probe insertions and demonstrated a preference for oral tube insertion. Oral insertion does require training and expertise in unsedated patients due to the tendency of individuals to gag during probe insertion. However, it was successfully inserted orally in all of our healthy

studies (any intolerance was due to distended balloon in the UOS region). Positioning of the catheter outside the teeth once the probe had been inserted orally minimised any impingement on swallowing.

Unlike previous studies, the EndoFLIP® was inserted trans-nasally by the researcher in participants with laryngectomy (Chapter 3.5.1). This change in protocol was made for two reasons; (1) patients were recruited from an outpatient ENT clinic and had already received a local anaesthetic to the nares and trans-nasal scope by their ENT surgeon within the previous hour and (2) these patients expressed a preference for trans-nasal probe insertion. This may have been due to the fact they were very used to trans-nasal probe insertions given their medical history, coupled with the fact a marked proportion of the participants had a history of oral regurgitation. It was observed that there was less gagging during the procedure compared to previous healthy studies, although this may have been due to desensitisation in the pharynges of patients with total laryngectomy.

Cook, Dodds, Dantas, Kern, Massey and colleagues evaluated the influence of an oral versus a naso-pharyngeal tube on swallowing in seven healthy adult males (199). They found that both liquid swallow types commonly observed in healthy individuals (i.e., "tipper" incisor-type swallows and "dipper" sublingual-type swallows) could be performed in subjects with naso-pharyngeal tubes. However, some individuals with oral tubes had difficulty initiating "tipper" swallows. Most importantly, authors found that timing of swallow events was not affected by presence or absence of a naso-pharyngeal or oro-pharyngeal tube.

Optimum insertion of the EndoFLIP® probe will be further deliberated in future studies in an effort to optimise tolerance, safety and accurate data acquisition. It is suspected that if balloon volumes are limited and safety aspect is addressed, trans-nasal insertion may anchor the balloon more securely in position and may be less likely to interfere with measurements of swallowing.

5.5.3.2. Use of local anaesthetic spray

Local anaesthetic was used in this research to ensure either the trans-nasal or trans-oral passing of the EndoFLIP® catheter was completed with minimal discomfort to subjects. The local anaesthetic was sprayed in the nares or onto the posterior pharyngeal wall preceding trans-nasal or trans-oral probe insertions, respectively. Local anaesthetic sprays are also frequently used in FEES and PM evaluations and it has been found to reduce discomfort levels (267). However, in a recent systematic review of eight randomised control trials, which included 746 participants, five out of eight included studies did not observe any advantage in using topical nasal anaesthetic sprays prior to FEES testing (268-273). In fact, they can lead to unpleasant effects such as altered taste (272).

As well as altered taste sensation, clinicians have repeatedly questioned if local anaesthetic to either the nares or posterior pharyngeal wall may interfere with the act of swallowing. Researchers have purported that nasal spray can distribute some of the anaesthesia to the pharyngeal mucosa, compromising sensory function and deglutition (274). Administration of local anaesthetic directly to the posterior pharyngeal wall surely ensures sensory and swallowing functions will be altered.

These issues indicate that perhaps a local anaesthetic should not be provided consistently without individual consideration. Instead, use of a lubricating gel, as was used in the studies in this thesis, may serve to alleviate discomfort during naso-pharyngeal insertion of a catheter. Where local anaesthetic needs to be administered, it may have less of an impact on swallowing if delivered to the nares.

5.5.3.3. Bolus Volumes and Consistencies

In these studies, the researcher sought to balance the acquisition of ample data with a prompt and efficient evaluation time to promote tolerance levels. Healthy studies were a maximum of twenty minutes in length (Chapter 4.2) while clinical (laryngectomy) studies were just ten minutes due to omission of postural strategies and manoeuvres from the study

protocol (Chapter 4.4.1). Future validation studies will determine the need for all aspects of the current study protocol.

In these studies, the effects of dry, 5ml and 10ml liquid swallows on UOS opening during swallowing were evaluated. Few other studies have investigated UOS opening during dry swallowing. This is due to the lack of barium contrast in the UOS region to measure opening patterns during VFS (203). No statistically significant difference in UOS opening was observed between 5ml and 10ml liquid swallows in this thesis. Many studies have identified a bolus volume effect, where larger bolus volumes increase UOS opening measures (44, 77, 84, 200, 253). Other researchers, who also did not establish a volume effect, have suggested the inclusion of more bolus volumes (e.g., 20mls) alongside 5 and 10ml bolus volumes to investigate this issue further (198). Numerous VFS and PM studies have examined the effects of multiple (often five) bolus volumes (i.e., 1-20mls) on UOS opening, amongst other swallow parameters. Perhaps the inclusion of one more bolus volume (e.g., 20ml) would establish a volume effect based on EndoFLIP® data.

To date, our study protocols have included only dry and liquid bolus consistencies. This was due to the fact that healthy volunteers attending for EndoFLIP® evaluation in the Neurogastroenterology clinic, Leuven, were fasting for subsequent barostat and HRM studies on the same day. Nonetheless, bolus consistency has been found to increase UOS opening during swallowing (84). Future studies should therefore examine the effects of other food consistencies (such as semi-solid or pudding consistency) on the duration and extent of UOS opening based on EndoFLIP® measures. This data would be of major clinical interest, especially as similar VFS studies evaluating the effect of bolus consistency are limited by the addition of barium sulphate to bolus consistencies.

Finally, it is proposed that bolus volumes and consistencies and any postures and manoeuvres under evaluation should be randomised in future study protocols to ensure that findings cannot be explained by any habituation or fatigue effect during the study protocol. A previous VFS study

demonstrated that swallow outcomes did not change with repeated swallows in healthy subjects (203). However, this may differ when a distended balloon is positioned in the UOS region.

5.5.3.4. Inclusion of Water Bolus when Testing UOS Opening during Swallowing

In this research, the author did not observe the effects of bolus volume on UOS opening during swallowing as measured by EndoFLIP®. This is despite the fact that increased UOS opening has been observed with increased bolus volumes during VFS and PM testing in previous studies, albeit inconsistently (76, 84, 200). Perhaps the passage of liquid through the UOS during water swallows alters EndoFLIP®measures of the extent UOS opening. The EndoFLIP® balloon may no longer be measuring wall opening alone as fluid has to pass between the balloon and the UOS wall. This issue needs to be examined more thoroughly in future testing as inclusion of the water bolus may nonetheless still be providing valuable information on duration of UOS opening and drop in IBP.

5.5.3.5. EndoFLIP® Balloon Volumes

Based on study findings to date, it appears that ramp distensions to a reduced balloon volume of 20ml are sufficient to safely challenge UOS compliance and to differentiate between healthy and disordered UOS tone. However, this will continue to be monitored further in future studies focusing on the effect of ageing and disease on UOS function.

Similarly, the 12ml balloon volume for swallow testing has been well tolerated to date. It appears to be an adequate volume to identify UOS opening patterns during swallowing. The researcher would be reluctant to increase the balloon volume for the swallow testing as it could affect tolerance levels and interfere with measures of UOS and swallow dynamics.

5.5.3.6. Swallowing during Ramp Distensions

Occasionally, subjects swallowed during ramp distensions in this research. This was informally noted to be more evident in the first of the two ramp distensions within the study protocol. It was also more apparent in healthy

subjects than in clinical studies which may reflect better pharyngeal sensation. The swallow events can impact markedly on both CSA and IBP measures during distensibility testing. This highlights the need to complete two ramp distensions during the study protocol to ensure subjects become habituated to the distended balloon in the UOS region. Researchers may then analyse data from the distension which is less confounded by swallow events. Alternatively, distensibility data can be smoothed out (i.e., data "binning" where a median value is selected from every ten measurements) to eliminate, or at least reduce, the effect of swallows on distensibility findings.

5.5.4. Data Analysis

5.5.4.1. Outcome measures

The outcome measures selected for analysis in the above research were clinically driven. In other words, dysphagia clinicians want objective information regarding the extent and duration of UOS opening during swallowing. Subsequently, this research focused on UOS diameter and duration of UOS opening. Nevertheless, based on studies completed it is apparent that EndoFLIP® provides information on several other aspects of deglutition which may be of clinical interest to dysphagia management. For example, the colour contour plots provide a quantitative measure of hyo-laryngeal excursion.

5.5.4.2. Increase Hertz rate (i.e., amount of data per second)

Currently, EndoFLIP® provides diameter, IBP and time data at a rate of 10Hz (10 measures per second). This contrasts to VFS which typically provides 25-29 frames per second during frame by frame analysis which is considered necessary due to the speed of events occurring during swallowing. The current hertz rate may therefore be a source of error in this research. Recent research has demonstrated that VFS frame rate can affect outcome measurement (275). This rate may have limited measures of extent and duration of UOS opening and minimum IBP as peak values may have been missed between measurements. Other studies have found that

the difference in duration of UOS opening across 2ml and 20ml bolus volumes can be less than 0.1 seconds (84).Despite this concern, a good range of values was apparent within the subject group. These values of UOS opening duration were also in keeping with previous VFS research (1, 78, 81). Given that swallow events are so rapid and that UOS opening occurs over a 0.5 second period, an increased rate of data acquisition may increase the sensitivity of EndoFLIP® measures and allow more aspects of swallowing to be detected. The small range of duration of UOS opening measures observed in this work and the lack of difference in duration of UOS diameter across bolus volumes may be explained by the slow rate of data acquisition by EndoFLIP®.

5.5.4.3. Minimum Detectable Diameter of EndoFLIP® probe

The minimal detectable diameter of the EndoFLIP® probe is 4.8mm (or 18.1mm^2) because of its physical size. Therefore, if the probe measures 4.8mm the actual value may be smaller. This is a source of error which may make the deviation of data for these small measurements seem less than they actually are and may be narrowing some UOS diameter data ranges. Additionally, EndoFLIP® does not provide real information on the actual luminal shape in the UOS region. However, from this and studies of other regions (i.e., OGJ), we know it is representative of function, particularly as it relates to the distension required to open the sphincter and representing that opening as a measure of multiple radial CSAs.

5.5.4.4. Colour Contour Plotting

As part of this research, EndoFLIP® measures of diameter, pressure and time were presented at rest and during swallowing events in colour contour plots (Figure 5.4). These plots provided a novel approach to the analysis of swallowing. It is anticipated that, based on date within colour contour plots, several new outcomes may be available to analyse swallowing parameters.

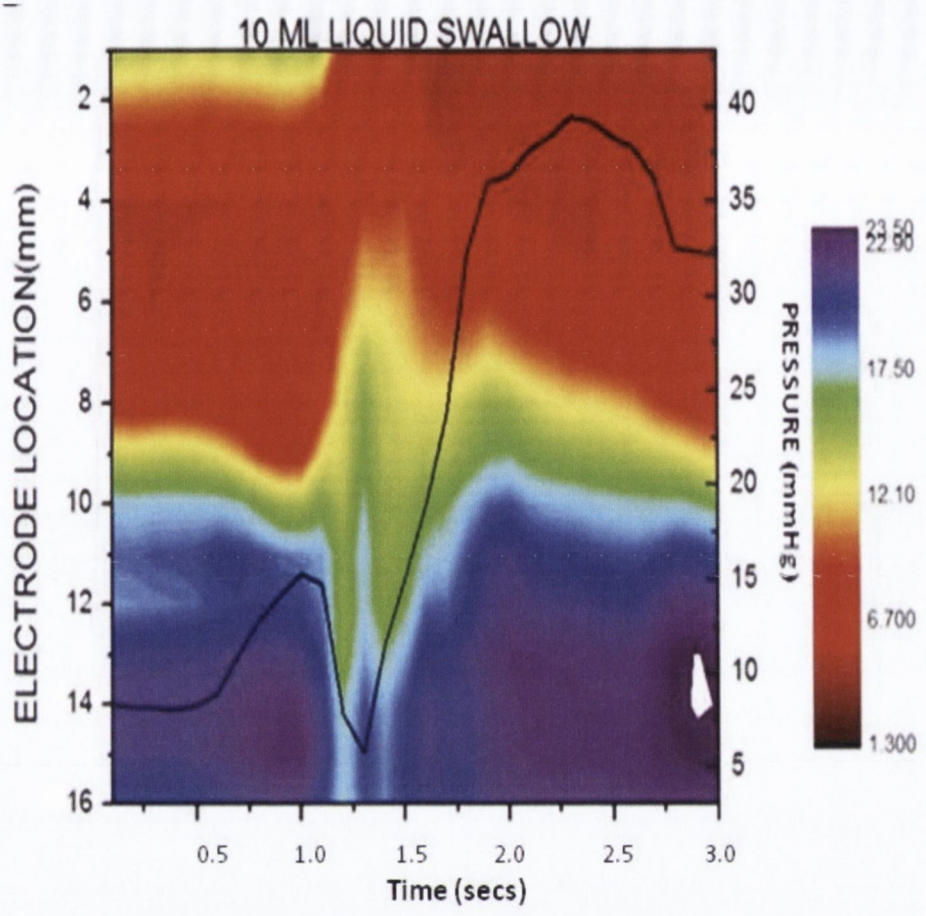

Figure 5.4 Colour Contour Plots of EndoFLIP® Data during Swallowing

If this colour contour plotting could be streamed in real-time on the EndoFLIP® screen during the procedure (as is observed during HRM procedures), it would be of considerable advantage to dysphagia clinicians. Additionally, live streaming of colour contour plots could serve as a useful biofeedback tool for patients with swallowing difficulties within therapy sessions. Surface EMG is already in use to encourage individuals with dysphagia to elicit "stronger" swallows. Colour contour plots based on EndoFLIP® data provide more information which may be visually more encouraging to both patients and clinicians.

5.5.4.5. Automated Analysis of Data

Manual extraction of quantitative data from all instrumental evaluations can be a laborious task and allows for the selection of incorrect values during swallow events (e.g., minimum IBP). The development of automated analysis of any instrumental evaluation can expedite patient evaluation. Automated analysis has already been developed in other dysphagia evaluations, including HRM and MII (276, 277). Based on data from 5ml swallows elicited by twelve healthy volunteers and three patients with dysphagia, researchers developed an algorithm in MATLAB (The MathWorks, Inc., Natick, MA) software to automatically extract data from regions of interests during swallow events captured by HRM spatiotemporal plots (276). This data strongly correlated with manually extracted data, thereby demonstrating the accuracy of the algorithm and improving the efficiency of data analysis. Perhaps in the longer term, automatic extraction of data from EndoFLIP® colour contour plots of swallow events may reduce the time required to analyse data and increase the number of parameters that can be measured.

5.5.5. Diagnostic Accuracy of EndoFLIP® for UOS Evaluation

All new diagnostic tests should be validated against a gold standard test. A gold standard diagnostic test is defined as having 100% sensitivity and specificity in detecting a target condition (see Table 5.2). While each of the diagnostic tests used in clinical dysphagia practice provide unique and valuable information on UOS opening in clinical practice, none of them can be deemed a true "gold standard" instrumental evaluation of swallowing.

Table 5.2 Aspects of a Diagnostic Test to be measured during Test Validation Process (278)

Feature of a test	Question which feature addresses
Sensitivity (true positive rate)	How good is the test at detecting people who aspirate or who have oro-pharyngeal dysphagia?
Specificity (true negative rate)	How good is this test at correctly excluding people who are not aspirating or who do not have oro-pharyngeal dysphagia?
Positive predictive value (Post-test probability of a positive test)	If a person tests positive, what is the probability that they do aspirate/have oro-pharyngeal dysphagia?
Negative predictive value (post-test probability of a negative test)	If a person tests negative, what is the probability that they do not aspirate/have oro-pharyngeal dysphagia?
Accuracy	What proportion of all tests have given the correct result (i.e. true positives and true negatives as a proportion of all results)?
Likelihood ratio of a positive test	How much more likely is a positive test to be found in a person with, as opposed to without, aspiration/dysphagia?

Identification of appropriate reference standards to validate new diagnostic tools such as EndoFLIP® can subsequently challenge dysphagia researchers. This obstacle is certainly not unique to dysphagia research and has also been encountered in many areas of medicine. Hence, validation studies are frequently performed where results from new tests are compared to a robust reference standard or a combination of reference standard tests (see FEES validation studies in Table 5.3). The selection of a suitable reference standard when validating a new diagnostic method should be made based on the specific parameter of swallowing being investigated (i.e., aspiration, residue or UOS opening).

Within the domain of oro-pharyngeal dysphagia, physiological evaluations being employed are at varying stages of validation (see Chapter 2.5). Some tools are either not yet at the diagnostic accuracy stage (e.g., accelerometry and tongue pressure), or, in the case of sonography and EMG, preliminary research has been conducted but no explicit diagnostic accuracy data has yet been published based on validation against a robust reference standard test (i.e., VFS or FEES). To provide an example of validation studies conducted on a well established evaluation, diagnostic accuracy studies conducted to validate FEES are outlined in Table 5.3.

Table 5.3 Studies Validating FEES against Videofluoroscopy[23]

Study	Dysphagia Parameter	Sensitivity, Specificity (+ 95% CI's where provided)	PPV & NPV (+ 95% CI's where provided)
(194)	Aspiration	Sensitivity 0.88. Specificity 0.92.	PPV 88%. NPV 92%.
	Pharyngeal residue	Sensitivity 0.93. Specificity 0.50.	PPV 75%. NPV 95%.
(220)	Aspiration	Sensitivity 22%. Specificity 97%.	PPV 78%. NPV 73%.
	Pharyngeal residue	Sensitivity 91%. Specificity 86%.	PPV 75%. NPV 95%.

[23] CI= confidence interval; PPV= positive predictive value; NPV= negative predictive value

(221)	11 parameters	Sensitivity 0.77. Specificity 0.88.	PPV 0.71. NPV 0.91
(222)	Pharyngeal propulsion	Sensitivity: 88.8% (95% CI=0.78, 0.99). Specificity: 62.5% (95% CI 0.46, 0.78).	PPV: 72.7% (95% CI 0.57, 0.87). NPV: 83.3% (95% CI 0.70-0.95)
	Aspiration	Sensitivity: 70% (95% CI= 0.54, 0.85). Specificity: 87.5% (95% CI=0.76, 0.98).	PPV: 70% (95% CI 0.54, 0.85). NPV: 87.5% (0.76-0.98)
(195)	Laryngeal elevation	Sensitivity= 1 (95% CI 0.3, 1). Specificity= 0.88 (95% CI 0.63, 0.94).	PPV=0.6 (95% CI 0.14, 0.94). NPV= 0.88 (0.63, 0.94).
	Pooling	Sensitivity= 0.88 (95% CI 0.63, 0.94). Specificity= 1 (95% CI 0.3, 1).	PPV=0.88 (95% CI 0.63, 0.94). NPV= 0.6 (0.14, 0.94).
	Aspiration	Sensitivity= 0.94 (95% CI 0.65, 0.89). Specificity= 1 (95% CI 0.29, 1).	PPV=0.91 (95% CI 0.72, 0.99). NPV= 0.86 (0.19, 0.99).
	Reflexive cough	Sensitivity= 1 (95% CI 0.69, 1). Specificity= 0.86 (95% CI 0.42, 0.99).	PPV=0.91 (95% CI 0.58, 0.99). NPV= 0.86 (0.42, 0.99).

(223)		Observer 1 Liquid Puree			Observer 2 Liquid Puree		Observer 1 Liquid puree			Observer 2 Liquid Puree	
	1.Early	Sens	44	11	67	56	PPV	44	20	43	63
	spillover	Spec	76	81	62	86	NPV	76	68	81	82
	2.Pharyngeal	Sens	83	80	67	40	PPV	50	62	44	44
	residues	Spec	79	75	79	75	NPV	95	88	91	71
	3.Laryngeal	Sens	56	0	56	0	PPV	33	0	39	0
	penetration	Spec	52	86	62	86	NPV	73	96	77	96
	4.Laryngeal	Sens	28	n/a	22	n/a	PPV	83	n/a	80	n/a
	aspiration	Spec	92	100	92	100	NPV	46	90	44	90

In order to determine the diagnostic accuracy (DA) of EndoFLIP®, sensitivity, specificity, positive and negative predictive values need to be obtained against a robust reference standard test (see Table 5.4.).

Table 5.4 EndoFLIP® Measures to be validated in Future UOS Research

EndoFLIP® Measure for Validation	**Robust Reference Standard Instrumental Examination**	**Measurement on references standard**
Extent and duration of UOS opening.	**VFS**	Extent and duration of UOS opening.
Extent and duration of UOS opening.		Penetration or Aspiration (using 8 point scale (279).
Extent and duration of UOS opening and minimum IBP during swallowing.		Pharyngeal residue.
Upward shift of UOS during swallow on colour contour plot.		Anterior & superior hyo-laryngeal excursion.
Increased UOS diameter preceding swallow on colour contour plot.	**Needle EMG to CP muscle**	Duration of CP relaxation during swallow.
Extent and duration of UOS Opening & minimum IBP during swallow.	**PM**	Extent and duration of UOS pressure drop during swallow.
Extent, duration of UOS opening and upward shift of UOS during swallow.	**HRM**	Extent, duration of UOS opening and upward shift of UOS during swallow.
Upward shift of UOS narrowing during swallow strip on colour contour plot.	**Surface EMG**	Anterior & superior hyo-laryngeal excursion.

Potential values and corresponding reference standards are proposed in Table 5.4. Specific measures of EndoFLIP® within colour contour plots and the most appropriate robust reference standards for these measures are proposed in Figure 5.5. In particular, it will be of interest to determine if EndoFLIP® is sensitive and specific to needle EMG measures of CP relaxation, as VFS and HRM are unable to differentiate between CP relaxation and UOS opening. This would be a major benefit to EndoFLIP® examination as accurate measurement of CP relaxation would guide dysphagia management. Data in this study also suggest that other pharyngo-oesophageal events such as the upward shift of the UOS during swallowing secondary to hyo-laryngeal excursion have the potential to be quantified based on these plots. This information may, in clinical practice, determine efficacy of or candidacy for rehabilitation (e.g., Shaker "head-lifting" exercises) or surgical interventions such as BoNT-A injections or CP myotomy (165, 262, 280).

When assessing the diagnostic accuracy of EndoFLIP® in UOS evaluation, several methodological issues (e.g., blinding of results, the selection of an acceptable reference standard, delay between diagnostic tests) should be considered. Numerous evaluation tools (e.g., Quality Assessment of Diagnostic Accuracy Studies or QUADAS tool) evaluate the methodological rigour of diagnostic accuracy studies and will serve to guide future diagnostic accuracy research (254). Also of note, measures of accuracy can vary across diagnostic groups. Future diagnostic accuracy studies of EndoFLIP® should include a wide spectrum of patients with varying severities of dysphagia (e.g., mild to gross aspiration) and at varying stages of disease processes.

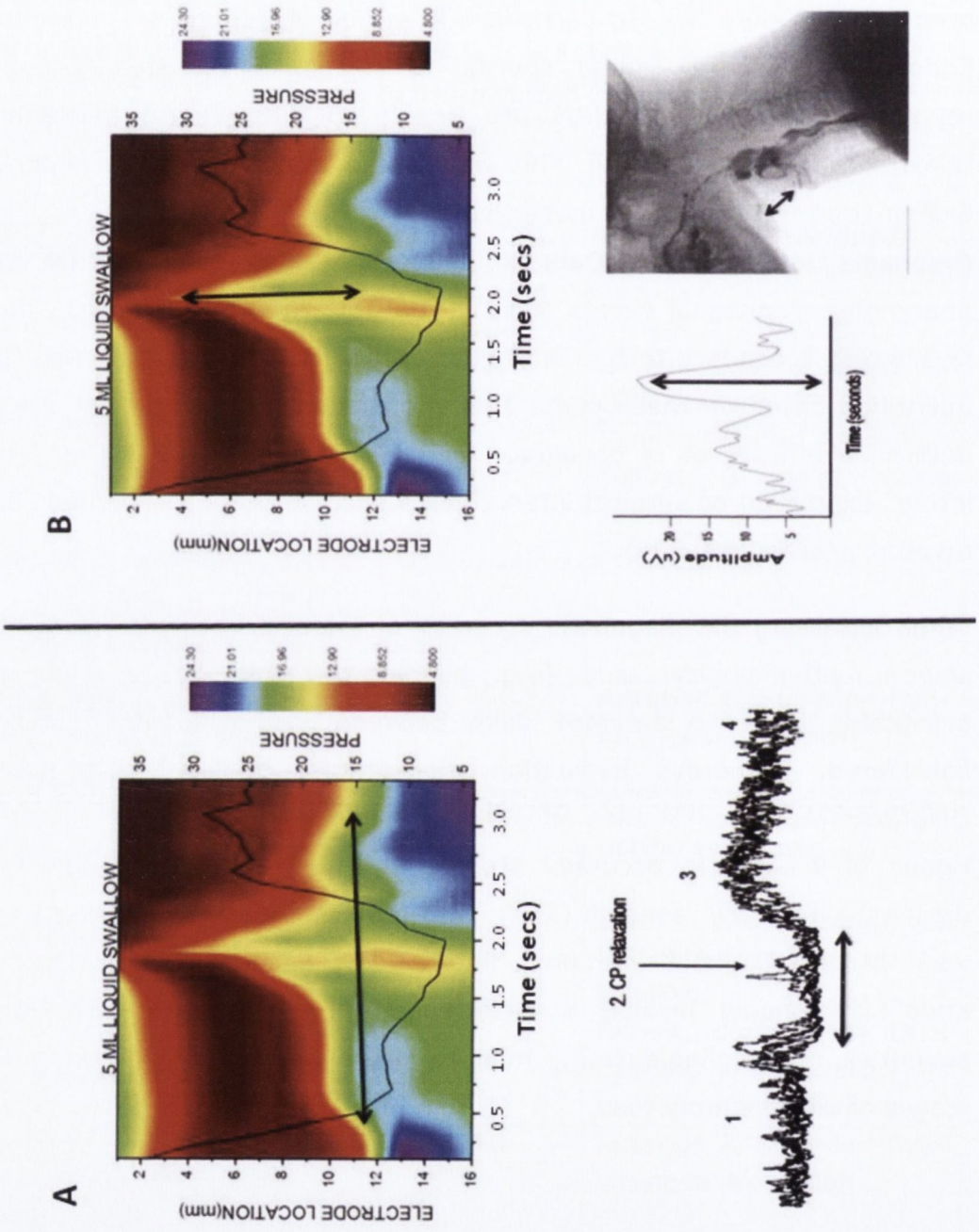

Figure 5.5 EndoFLIP® Data in Colour Contour Plots proposed for Validation against needle (A) and surface (B) EMG

While diagnostic accuracy is a vital element in the development of a new diagnostic tool, it is not the only parameter which should be focused on by researchers. Other issues such as adverse events, tolerability, cost-effectiveness, diagnostic yield and speed of analysis should contribute to the value of a new diagnostic test. In fact, tests without diagnostic accuracy aren't without advantages. If they are practical, cheap, convenient, easy to perform and interpret and accessible, they may be an initial port of call in order to determine the need for a gold standard test, especially if that gold standard test is expensive or involves radiation.

5.5.6. Where is EndoFLIP® as a Clinical Assessment of Dysphagia?

EndoFLIP® has already proven in this research to be a portable tool which provides easy to analyse quantitative measures of UOS function without need for radiation. Nevertheless, the work presented in this thesis has been preliminary in terms of the research required to validate EndoFLIP® as a robust clinical dysphagia assessment. Many questions remain regarding the diagnostic accuracy and clinical utility of this tool (see Chapter 5.5.5). While many questions remain regarding the role of EndoFLIP®, it is not far behind other UOS assessment tools such as HRM and MII. Research behind both of these diagnostic tools is currently limited to small cohort studies and they present with limited information regarding diagnostic accuracy. In this era of evidence-based practice, it would be erroneous to introduce EndoFLIP® too quickly into clinical practice. However, once further validation work has been completed, it is anticipated that it will serve a valuable role in accurately establishing candidacy for various dysphagia treatments outlined in Chapter 2.4 and in objectively determining the benefits of those interventions. In turn, the evidence-base for the growing number of dysphagia interventions may grow markedly and the nature of those treatments may be refined.

5.5.7. Long Term Goal

Once appropriate validation research has been completed, sensitivity and specificity of EndoFLIP® data against dysphagia parameters such as aspiration and pharyngeal residue on VFS will be identified. The ability of EndoFLIP® to identify the underlying cause of impaired UOS opening (i.e., CP relaxation or hyo-laryngeal excursion) will also be investigated. Based on this research, EndoFLIP® may be employed clinically to screen patients with dysphagia in ward settings or outpatient clinics. Its portability would allow flexibility in terms of evaluation setting. This would be particularly advantageous in those patients who cannot be transferred to radiology or in settings where there is no access to VFS. This introduction to clinical practice may reduce waiting lists for VFS or FEES and may speed up the delivery of both inpatient and outpatient dysphagia care. As already alluded to in the first chapter in this thesis, the ultimate goal of the introduction of a new diagnostic tool would be to reduce the clinical complications, the alterations to quality of life and healthcare costs associated with dysphagia.

5.6. CONCLUSIONS

The aim of this research was to establish the role of EndoFLIP® in UOS evaluation. The addition of novel quantitative data using a user friendly, cost effective, non-radiological portable device may help to advance our knowledge of UOS function in dysphagia practice. This thesis presented the first piece of research conducted to explore the role of EndoFLIP® in evaluating UOS function. The findings from this research contribute novel quantitative information relating to UOS function and opening patterns during swallowing. These findings are currently lacking in clinical practice and may serve to establish candidacy for and effectiveness of various dysphagia interventions. All the while, this data was obtained from a portable tool at the bedside without need for radiation.

Specific conclusions include:

1. EndoFLIP® is a highly accurate measuring tool for determining the geometry of sphincteric regions under controlled distension. Diameter measurements obtained by EndoFLIP® are adequately reproducible across varying balloon constrictions and transducer positions. The EndoFLIP® diameter measurements obtained under varying constraints and whilst manipulated through sharp angles were highly accurate.
2. The EndoFLIP® balloon originally designed to measure OGJ compliance, with a length of 10cm and maximal diameter of 2.5cm, was safely positioned and distended in the UOS region of patients with dysphagia by the researcher without any airway impingement under VFS. Hence this balloon design was selected for evaluation of the UOS. The researcher developed a study protocol specific to UOS evaluation and defined outcome measures pertaining to UOS distensibility and UOS opening during swallowing.
3. Good tolerance (13/14) of UOS distensibility testing was observed in healthy non-elderly adults. During 20ml ramp distensions, UOS CSA plateaued from 10ml balloon volume and intra-balloon pressure increased significantly from 10ml to 20ml balloon volume, indicating healthy UOS tone. A gender difference in EndoFLIP® measurements of UOS distensibility was observed.
4. Quantitative measures of extent and duration of UOS opening and minimum IBP during swallowing were also obtained in fourteen non-elderly healthy subjects using EndoFLIP®. UOS opening measures were comparable to VFS measures of UOS opening during swallowing found in previous studies. Gender differences in UOS opening measures were identified. EndoFLIP® data was used to create colour contour plots of swallow events which provide a novel means to visualise UOS patterns during swallowing.
5. The effect of voluntary postural strategies and manoeuvres commonly employed in dysphagia practice on UOS opening were investigated in eleven healthy subjects using EndoFLIP®. The Mendelsohn manoeuvre significantly increased duration of UOS opening and the supraglottic swallow significantly reduced minimum IBP during swallowing.

6. In order to initiate the diagnostic accuracy process, EndoFLIP® measures of UOS opening during swallowing were compared to AIM analysis parameters based on combined HRM-MII (n=11). A significant interaction effect correlation was observed between EndoFLIP® extent of UOS opening and pressure at nadir impedance (PNadImp) (p=0.034). A significant interaction effect correlation was also identified between EndoFLIP® UOS opening duration and UOS relaxation interval (RI) (p=0.0272). A significant volume dependent effect was observed between EndoFLIP® UOS Opening Duration and time from nadir impedance to peak pressure (TNadImp-PeakP) (p=0.0269), which was significant on 5ml liquid swallows (p=0.0117).
7. EndoFLIP® was used to evaluate distensibility of the reconstructed pharyngo-oesophageal segment (POS) in ten patients with total laryngectomy. A 70% (7/10) tolerance rate of EndoFLIP® evaluation was observed. The significant increase in POS CSA throughout the 20ml ramp distension suggested reduced POS tone compared to UOS tone in healthy controls. The POS opened less during swallowing across bolus volumes, albeit insignificantly. Duration of POS opening during swallowing was significantly longer across bolus volumes than duration of UOS opening in healthy controls.
8. Based on an online international survey of dysphagia-trained clinicians with varying levels of clinical experience, there is marked dissatisfaction with UOS evaluations currently available in dysphagia practice.

When taken together, results from these studies in this thesis justify further work to clarify and develop the role of EndoFLIP® in clinical dysphagia practice.

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APPENDICES

APPENDIX 1. Patient Information Leaflet

Use of the Functional Lumen Imaging Probe (FLIP) to Evaluate Upper Oesophageal Sphincter Function

THE ADELAIDE & MEATH HOSPITAL, DUBLIN
INCORPORATING
THE NATIONAL CHILDREN'S HOSPITAL

Introduction

The purpose of this research project is to find out if an evaluation tool called the FLIP probe can be used to assess swallowing for eating and drinking. The study will be divided into three parts:

i) an adapted FLIP probe will be placed in a small group of people who are already attending hospital for an x-ray examination of swallowing (videofluoroscopy). This is to ensure safe and effective placement of the probe.
ii) the FLIP probe will be used to gather information in a group of people who do not have any difficulty swallowing.
iii) the FLIP probe will be used to evaluate swallowing in a group of people who have difficulty eating and drinking.

Procedures

Men and women of various ages will be asked to participate in this study. People recruited for the study will be asked to attend the hospital for one forty-five minute appointment. During this appointment, the participant will have a small probe placed via the nose or mouth into the oesophagus (gullet). Once the probe is in place, the researcher will collect data when the participant is in a resting position. Participants will also be asked to carry out a simple manoeuvre while the probe is in place (i.e., turning head to one side).

Benefits

For people with no swallowing difficulties, this study may have no direct benefit to the individual participant but the results may benefit subsequent patients. For people with swallowing difficulties, any identified impairment will be followed up clinically, if desired.

Risks

Adverse events are not anticipated during the procedure. Very infrequent events while the probe is being placed via the nose or mouth include mild discomfort, nose bleeds, fainting episodes and airway obstruction if the tube is inserted in the wrong place. *If the tube is in the wrong place it may cause*

airway obstruction. These are unlikely to occur. A doctor will be present while tubes are being put in place.

Exclusion from participation (healthy volunteers in part (ii) of study only)

Your speech and language therapist has told you that you cannot be in this study if any of the following are true:

- you have a history of swallowing difficulties
- you have a history of any medical illness affecting neuromuscular function, respiratory or gastrointestinal disease (i.e., GORD, achalasia), or structural disorder
- You are on medication affecting neuromuscular function

Alternative treatment

You do not have to be a part of this study to be treated. There are other assessments available that can be used to treat your complaint and your speech and language therapist has discussed this with you.

Confidentiality

Your identity will remain confidential. Your name will not be published and will not be disclosed to anyone outside the hospital.

Compensation

Your doctors are covered by standard medical malpractice insurance. Nothing in this document restricts or curtails your rights.

Voluntary Participation

You have volunteered to participate in this study. You may quit at any time. If you decide not to participate, or if you quit, you will not be penalised and will not give up any benefits which you had before entering the study.

Stopping the study

You understand that your doctor or the sponsoring company may stop your participation in the study at any time without your consent.

Permission

This study has hospital Research Ethics Committee approval

Further information

You can get more information or answers to your questions about the study, your participation in the study, and your rights, from Julie Regan, Speech & Language Therapist, who can be telephoned at 01 4142776. If your clinician learns of important new information that might affect your desire to remain in the study, she will tell you

APPENDIX 2. Participant Consent form

Use of the Functional Lumen Imaging Profile (FLIP) to evaluate Upper Oesophageal Sphincter Function

I, ..., have read and understood the patient information leaflet for participants on the above named research study and have discussed it with the researcher.

I freely choose to participate in this study and understand that I can withdraw without compromise at any time.

I also understand that the research study is strictly confidential.

I hereby agree to participate in this research study.

Participant Signature:.....

Participant Name: .....

Date:.....

Statement of investigator's responsibility: I have explained the nature, purpose, procedures, benefits, risks of, or alternatives to, this research study. I have offered to answer any questions and fully answered such questions. I believe that the participant understands my explanation and has freely given informed consent.

Clinician's signature:.....
Date:.....

APPENDIX 3. Health Screen for Healthy Volunteers

Background information

Date		Height (inches)			
Pt code		Weight (kgs)			
Age (18+)		Neck circumference			
DOB (d/m/y)		C2H5OH? (Y/N)		If Y, units p/wk	
Gender (m=1;f=2)		Smoker? (Y/N)		If Y, cigs p/day?	

Exclusion criteria

	Does volunteer have a history of:	**Yes**	**No**
1	Oro-pharyngeal or oesophageal dysphagia		
2	Gastro-oesophageal reflux disease		
3	Achalasia		
4	Hiatus hernia		
5	Oesophageal stricture/ web/ diverticulum		
6	Oesophageal perforation or tear		
7	Oesophageal surgery		
8	Respiratory disease (i.e., COPD; lung Ca; tracheostomy tube)		
9	Stroke/ transient ischaemic attack		
10	Head injury		
11	Idiopathic inflammatory myopathy		
12	Any other central or peripheral nervous system disorder		
13	Speech/ voice disorder (e.g., dysarthria, vocal cord palsy)		
14	Head, neck or oesophageal cancer		
15	Radio/chemotherapy to head, neck or oesophageal region		
	Is volunteer on any of the following medications?	**Yes**	**No**
16	Medication affecting UOS neuromuscular transmission (e.g., Botox)		
17	Warfarin		
18	Antipsychotic medication		
19	Any other medication known to affect swallowing		
	Additional question for female participants	**Yes**	**No**
20	Is volunteer pregnant or suspect she may be pregnant?		

Summary

	Yes	**No**
Does volunteer present with any exclusion criteria outlined above?		
Is volunteer in good health/medically suitable to participate in study?		

Signature:_____

APPENDIX 4. Letters of Ethical Approval

(Tallaght Hospital, Dublin and University Hospital, Leuven, Belgium)

THIS NOTEPAPER MUST NOT BE USED FOR PRESCRIPTIONS OR INVOICING PURPOSES

THE ADELAIDE & MEATH HOSPITAL, DUBLIN
INCORPORATING
THE NATIONAL CHILDREN'S HOSPITAL

TALLAGHT, DUBLIN 24, IRELAND
TELEPHONE +353 1 4142000

SJH/AMNCH Research Ethics Committee Secretariat
Dan Lynch Ph: 4142860 email: Dan.Lynch@amnch.ie
Ursula Ryan Ph: 4142342 email: Ursula.Ryan@amnch.ie
Secretariat Fax 4142371

Ms. Julie Regan
Clinical Specialist Speech & Language Therapist
Adelaide & Meath Hospital
Tallaght
Dublin 24

April 6th 2009.

REC reference: 2009/03/13

(Please quote REC reference and EudraCT number on all correspondence)

Re: Adaption of the Functional Lumen Imaging Profile (FLIP) to Examine the Upper Esophageal Sphincter in Neurogenic Dysphagia.

Dear Julie,

The SJH / AMNCH Research Ethics Committee reviewed the above application at its meeting held on March 25th 2009

The Committee has given a favourable ethical opinion for the above study, based on the application form, protocol and supporting documentation subject to the following conditions:

- The Patient Information Leaflet should be on headed paper.
- The Patient Information Leaflet should include the following risk: "*if the tube is in the wrong place it may cause airway obstruction*". In this regard the Patient Information Leaflet should give an assurance that a doctor will be present while the tube is being put in place.

Yours sincerely,

Dr. Ray McDermott,
Chairman,
SJH/AMNCH Research Ethics Committee.

COMMISSIE MEDISCHE ETHIEK VAN DE UNIVERSITAIRE ZIEKENHUIZEN KULEUVEN
U.Z. GASTHUISBERG E330
HERESTRAAT 49
B-3000 LEUVEN (BELGIUM)

KATHOLIEKE
UNIVERSITEIT
LEUVEN

Aan Prof. J. Tack
Gastroenterologie, UZ Leuven

NMERK ML7490
EUVEN, 29 juni 2011

Karakterisering van de motoriek, sensitiviteit en opening van de bovenste slokdarmsfincter bij gezonde volwassenen tijdens slikken.

Belgisch Nummer B322201111656

S53356

Studiefase

DEFINITIEF GUNSTIG ADVIES

Geachte Collega,

De Commissie Medische Ethiek van de Universitaire Ziekenhuizen K.U.Leuven heeft vermeld protocol onderzocht en besproken op haar vergadering van 17 juni 2011.

Na inzage van de bijkomende informatie en/of aangepaste documenten met betrekking tot vermeld dossier (uw schrijven van 27 juni 2011) is de Commissie van oordeel dat de voorgestelde studie, zoals beschreven in het protocol, wetenschappelijk relevant en ethisch verantwoord is. Ze verleent dan ook een gunstig advies over deze studie.

Dit gunstig advies betreft onder meer:

- Informatie- en toestemmingsformulier voor de deelnemer: aangepaste versie ontvangen op 27/6/2011
- Protocol: versie 1 dd 17/05/2011

De Commissie bevestigt dat ze volgens de ICH-GCP principes werkt (International Conference on Harmonization Guidelines on Good Clinical Practice).

Nota:

Dit gunstig advies van de Commissie houdt niet in dat zij de verantwoordelijkheid voor de geplande studie op zich neemt. U blijft hiervoor dus zelf verantwoordelijk. Bovendien dient U er over te waken dat uw mening als betrokken onderzoeker wordt weergegeven in publicaties, rapporten voor de overheid enz., die het resultaat zijn van dit onderzoek.

U wordt eraan herinnerd dat bij klinische studies iedere door U waargenomen ernstige verwikkeling onmiddellijk zowel aan de opdrachtgever (desgevallend de producent) als aan de commissie medische ethiek moet worden gemeld, ook al is het oorzakelijke verband met de studie onduidelijk.

SECRETARIAAT: M. LEYS N. OPDEKAMP D. VAN MOLL M. SAELENS M. VERBEECK H. HUYGHE
Tel +32 16 34 86 00 Fax +32 16 34 86 01 ec@uzleuven.be ec-submission@uzleuven.be www.uzleuven.be/ec

ILAD NR . 2

KENMERK ML7490
KENMERK
LEUVEN . 29 juni 2011

Indien de studie niet binnen het jaar beëindigd is, vereist de ICH-GCP dat een jaarlijks vorderingsrapport aan de commissie wordt bezorgd.

Tenslotte verzoeken wij U ons mee te delen indien een studie niet wordt aangevat, of wanneer ze wordt afgesloten of vroegtijdig onderbroken (met opgave van eventuele reden).

Indien er een Clinical Trial Agreement is, kan de studie in ons centrum pas aangevat worden wanneer dit Clinical Trial Agreement goedgekeurd en ondertekend werd door de gedelegeerd bestuurder van UZ Leuven.

Met de meeste hoogachting,

Prof. Dr. Walter VAN DEN BOGAERT
Voorzitter Commissie Medische Ethiek
UZ K.U.LEUVEN

Prof. Dr. W. Van den Bogaert
Voorzitter
Commissie Medische Ethiek van de UZ K.U.Leuven

Cc : **FAGG** (Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten)
Departement R&D
Eurostation, blok 2
Victor Hortaplein 40, bus 40
B-1060 Brussel

Clinical Trial Center (CTC), UZ Leuven, Campus Gasthuisberg

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COMMISSIE MEDISCHE ETHIEK VAN DE UNIVERSITAIRE ZIEKENHUIZEN K.U.LEUVEN
TOETSINGSCOMMISSIE
UZ GASTHUISBERG E330
HERESTRAAT 49
3000 LEUVEN BELGIUM

KATHOLIEKE
UNIVERSITEIT
LEUVEN

ONS KENMERK
UW KENMERK
LEUVEN,

Ledenlijst Commissie Medische Ethiek/Toetsingscommissie (OG032)
vanaf 6 mei 2011 tot op heden
List of Members Ethics Committee/IRB (OG032)
from May 6th 2011 till present

Prof. Walter Van den Bogaert, M.D.	Chairman (M)	Radiotherapy-Oncology
Dr. Johan Wildiers, M.D.	Vice-Chairman (M)	Medical Oncology
Dr. Sabine Graux, M.D.	Secretary (F)	Physician
Dr. Sonja Haesendonck, M.D.	Secretary (F)	Physician
Prof. Xavier Bossuyt, M.D.	Member (M)	Immunology
Prof. D. Bullens, M.D.	Member (F)	Paediatrics
Prof. Willem Daenen, M.D.	Member (M)	Cardiac Surgery
Dr. Lut De Groote, M.D.	External Member (F)	General Practitioner
Prof. Jan de Hoon, M.D.	Member (M)	Clinical Pharmacology
Prof. Walter Heyns, M.D.	Member (M)	Experimental Medicine
Prof. Peter Lauwers, M.D.	Member (M)	Intensive Care
Dr. Ben Van Calster	Member (M)	Statistics
Prof. Jan Van Hemelrijck, M.D.	Member (M)	Anesthesiology
Prof. Guido Verhoeven, M.D.	Member (M)	Experimental Medicine
Prof. Jozef Vermylen, M.D.	Member (M)	Internal Medicine
De heer Paul Vranckx	Member (M)	Head Nurse
Mrs. Karlien Wouters, Law	Member (F)	Medical Legislation

(M) = Male (F) = Female

De Commissie voor Medische Ethiek volgt de voorschriften van ICH Good Clinical Practice en de lokale wettelijke bepalingen terzake (wet van 7 mei 2004 inzake experimenten op de menselijke persoon en bijbehorende KB's en programmawet)

The Ethics Committee operates according to ICH Good Clinical Practice and local applicable regulations.

FLIP PROTOCOL FOR UOS EVALUATION

Subject Code:_____ Date:_____

A. UOS DISTENSIBILITY (2x 20ml ramp distensions)

1. START TIME ON FLIP SCREEN:	2. START TIME ON FLIP SCREEN:

B. SWALLOWS ACROSS DIFFERENT BOLUS VOLUMES (12ML BALLOON VOLUME)

HEAD NEUTRAL POSITION

AT REST	AT REST	DRY SWALLOW	DRY	5ML SWALLOW	5ML SWALLOW	10ML SWALOW	10ML SWALLOW

CHIN TUCK POSITION

AT REST	AT REST	DRY SWALLOW	DRY	5ML SWALLOW	5ML SWALLOW	10ML SWALOW	10ML SWALLOW

HEAD TURN LEFT POSITION

AT REST	AT REST	DRY SWALLOW	DRY	5ML SWALLOW	5ML SWALLOW	10ML SWALOW	10ML SWALLOW

APPENDIX 6. Current UOS Evaluation Survey

Section A- Demographic Section

1. Please state your staff position (or equivalent where terminologies differ)

Basic grade SLT, Senior SLT, Clinical Specialist SLT, SLT Manager, Research SLT

2. What is your clinical experience in years?

1-5, 6-10, 11-15, 16-20, >20

3. Where are you based?

Ireland, UK, Europe (outside ROI/UK), USA, Canada, Australia, NZ

4. What setting are you working in?

Acute hospital, Rehabilitation setting, University/3rd Level Education, Community Care Setting, Private Practice, Other

5. What is your caseload?

Adults, Paediatrics, Both

6. Do you have a dysphagia caseload?

Yes, No

7. What percentage of your clinical caseload is dysphagia?

0-19%, 20-39%, 40-59%, 60-79%, 80-100%

Section B- Current Evaluation of the Upper Oesophageal Sphincter

8. Have you received certified training in the following?

Videofluoroscopy, FEES, Pharyngeal manometry, Surface EMG, Other

9. Which of the following dysphagia evaluations are available at your work setting?

Videofluoroscopy, FEES, Pharyngeal Manometry, Needle EMG of CP muscle

10. Which examination do you think provides the most useful information regarding upper oesophageal sphincter (UOS) opening during swallowing?

Videofluoroscopy, FEES, Pharyngeal Manometry, Needle EMG

11. Are you satisfied with the accuracy and reliability of evaluations currently available to measure UOS function?

Yes, No, Don't Know

12. Do you experience any challenges in evaluating UOS function?

Yes, No, Don't Know

13. If yes, what is the biggest challenge when investigating UOS dysfunction?

Lack of resources/equipment, Lack of training, Lack of multidisciplinary team, Lack of knowledge, Lack of reliability, Lack of quantitative information, None of the above.

Section C- Functional Lumen Imaging Probe

14. What aspects of FLIP data would be useful in your management of dysphagia?

3D image of UOS; Quantitative information re. cross-sectional area of UOS, Quantitative information regarding length of UOS, Pressure data, Not sure, No aspects useful

15. How do you think the data provided by FLIP would be of value in your assessment and management of dysphagia?

No value; To monitor progress of disease ; To monitor spontaneous recovery ; To ascertain benefit from compensatory strategies ; To establish candidacy for intervention; To determine efficacy of intervention

16. Do you think FLIP has advantages over videofluoroscopy or manometry in evaluating UOS function?

Yes, No, Don't Know

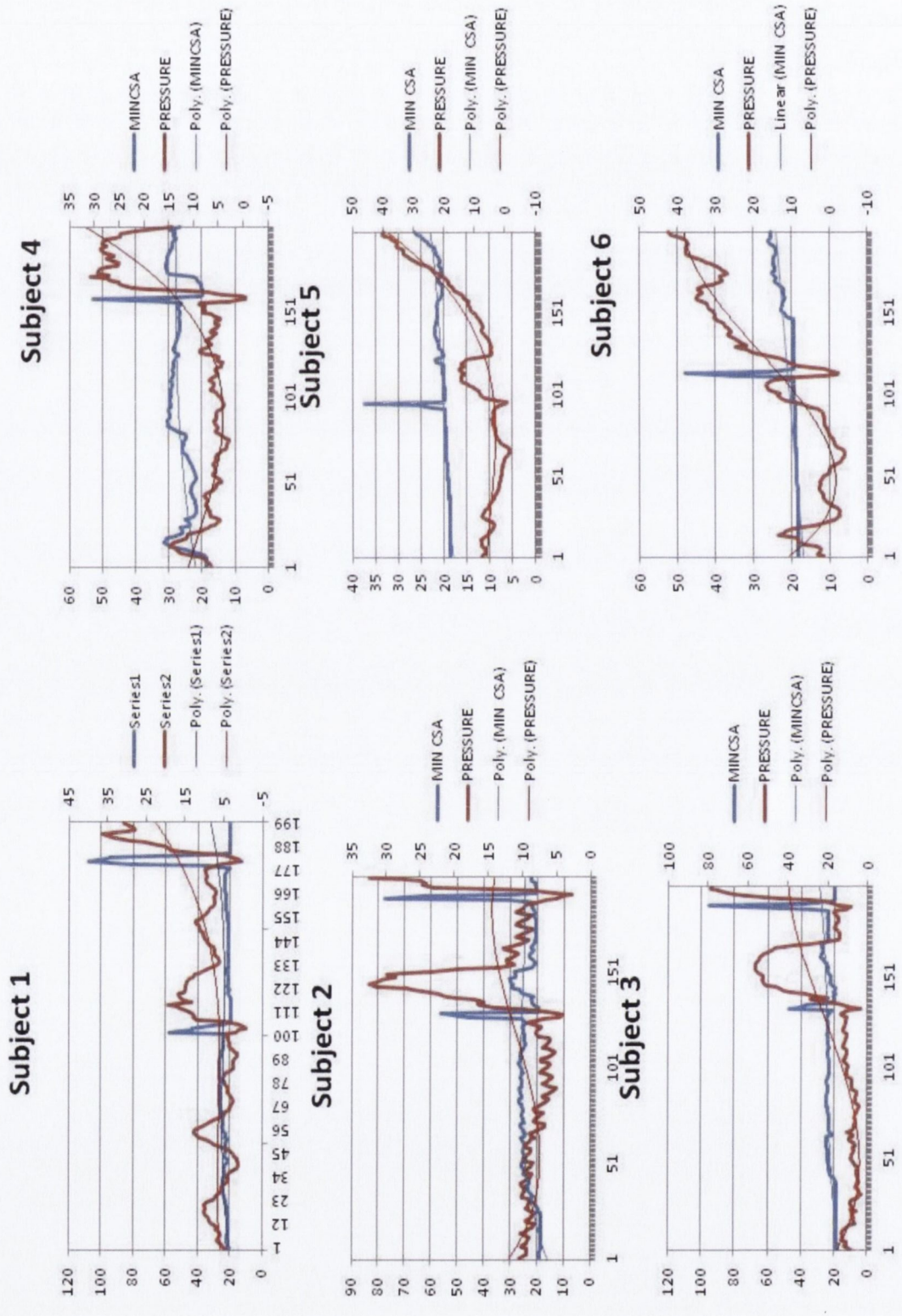
If so, please state what advantages FLIP has in evaluating UOS function

Visual imagery, Objective data, Reliable data, Quantifies effect of intervention, Measures extent of UOS opening, Not sure

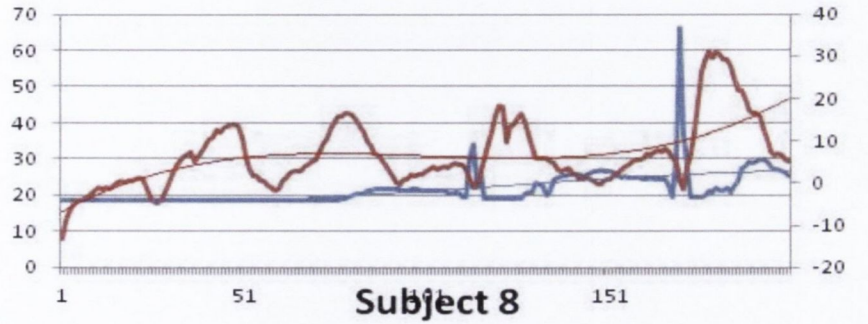
APPENDIX 7. Audio-Visual Clips

1. Trans-nasal insertion of EndoFLIP® probe under videofluoroscopy (Chapter 4).
2. Trans-oral insertion of EndoFLIP® probe during healthy volunteer studies without videofluoroscopic guidance (Chapter 4).
3. Study Protocol for UOS Evaluation using EndoFLIP® (Chapter 4)
4. Changing Geometric Profile of UOS on EndoFLIP® Screen during Study Protocol (Chapter 4)
5. Subject attending for Combined High Resolution Manometry and Multi-Channel Intra-Luminal Impedance post EndoFLIP® examination as part of Comparison Study (Chapter 4).

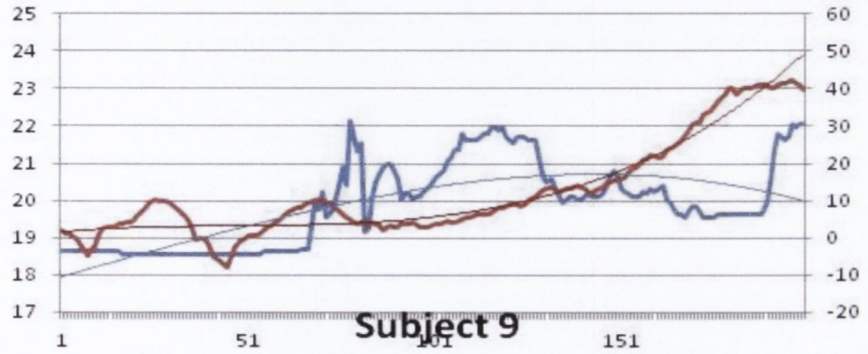
APPENDIX 8. Individual UOS Distensibility Graphs



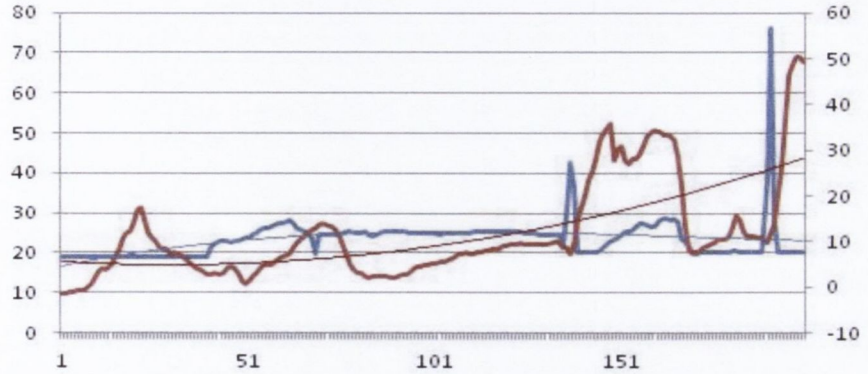
Subject 7



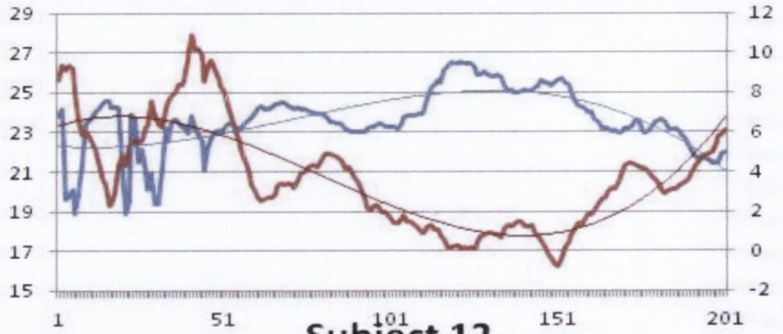
Subject 8



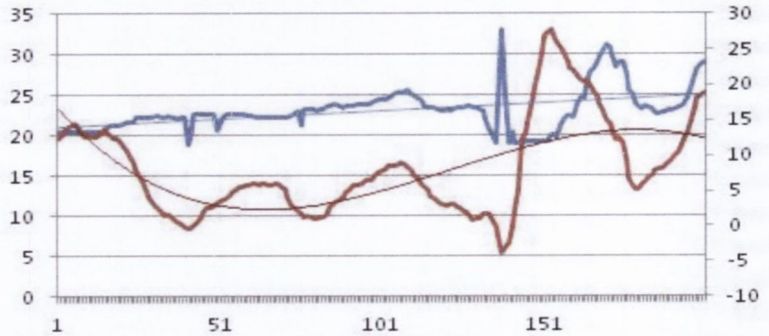
Subject 9



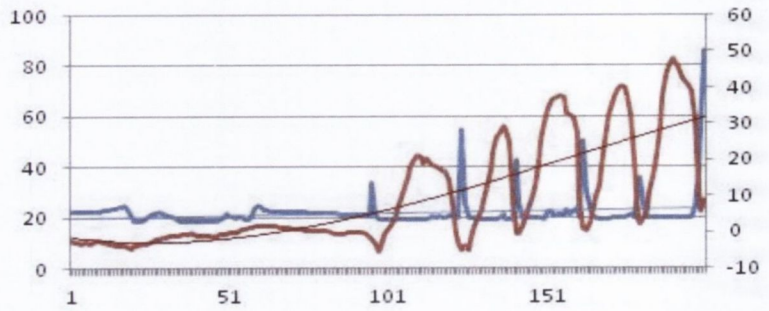
Subject 10



Subject 12



Subject 13



APPENDIX 9. Poster Presentations

1. Regan, J., Walshe, M. & B.P. McMahon. Working Towards an Objective and Reliable Evaluation of the Upper Esophageal Sphincter. United Kingdom Swallow Research Group (UKSRG). UCL Institute of Child Health, London, UK. 4-5th February 2010. (1st poster prize)

2. Regan, J., Walshe, M. & B.P. McMahon. Current Evaluation of the Upper Esophageal Sphincter in Neurogenic Dysphagia- A Survey, 6th Congress of the European Union Geriatric Medicine Society (EUGMS). Dublin, September 2010.

3. Regan, J., Walshe, M. & B.P. McMahon. Challenges in Evaluating the Upper Esophageal Sphincter in Dysphagia Practice- A Survey of SLPs. Dysphagia Research Society 18th Annual Conference. San Antonio, Texas. March 2011.

4. Regan, J. and B.P. McMahon, T1907 A Novel Distensibility Technique for Measuring Upper Esophageal Function-Pilot Data. Gastroenterology, 2010. 138(5): p. S-604-S-604.

5. Regan, J., Walshe, M. & B.P. McMahon. Distensibility Testing using the Functional Lumen Imaging Probe to Measure Duration and Extent of UES Opening - Preliminary Data. Journal of Clinical Gastroenterology: February 2011 - Volume 45 - Issue 2 - pg 181-201.

6. Regan, J., Walshe, M., Rommel, N., Tack, J. & McMahon, B. Distensibility of the Upper Esophageal Sphincter in Healthy Subjects using EndoFLIP®. OESO Conference. Italy, September, 2012.

Working Towards an Objective and Reliable Evaluation of the Upper Esophageal Sphincter

Regan, J.[1,3], Walshe, M.[2] & McMahon, B. P.[3,4]

1 Speech & Language Therapy Department, Adelaide and Meath Hospital, Tallaght, Dublin 24, Ireland
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Upper Esophageal Sphincter (UES)

A muscular constriction forming a barrier between pharynx and esophagus (see Figure 1). UES relaxes intermittently to allow transphincteric flow of fluid or gas during orthograde (e.g. swallowing) and antegrade (e.g. emesis or belching) events (see Figure 2).

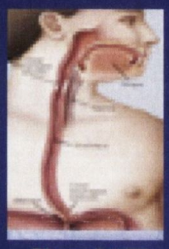
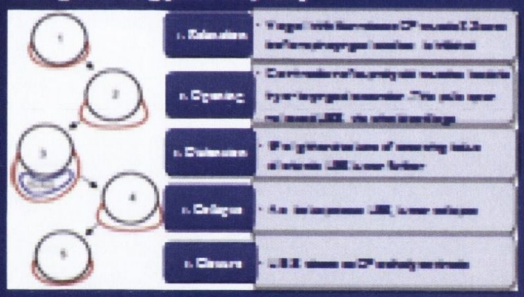


Figure 1. UES

Figure 2. Phases of UES Opening During Swallowing (Jacob et al., 1997)



Impaired UES Opening

Associated with numerous neurological conditions (e.g. stroke, PD, MND). It can prevent food, drinks and saliva from being transported safely and efficiently from the pharynx into the oesophagus during swallowing. This leads to serious respiratory and nutritional complications and to compromised quality of life.

Existing diagnosis of impaired UES opening is substandard (see Table 1). Limitations to current evaluations are resulting in frequent misdiagnosis and mismanagement of impaired UES opening in people with neurogenic dysphagia.

Table 1. Limitations to Current UES Evaluations

Videofluoroscopy	-Poor inter-rater reliability in diagnosing UES dysfunction
Pharyngeal Manometry	-Drop in UES pressure indicates sphincter no longer squeezing on probe sensor. This pressure change gives no information re. accent of UES opening which is of major relevance to swallowing -Great variability in normal ranges of UES pressure due to influence of age, gender, emotional state, bolus volume and consistency -Sensor placement influences readings as UES pressure profile asymmetric -Manometry findings not predictive of treatment success in myotomy studies. Manometry findings change diagnosis in only 33% of patients and alter management in just 40%
Endoscopy	-Provides no information regarding patency of the UES for the oncoming bolus

Methodology

The Functional Lumen Imaging Profile (FLIP) is an objective evaluation tool based on impedance planimetry. It can obtain multiple diameter measurements of a lumen (e.g. UES, ano-rectal region) and convert these measurements into a three-dimensional image (see Figure 3). Authors hypothesised that the FLIP probe could be adapted to evaluate UES function and ultimately strategies used to modify function.

Figure 3. Functional Lumen Imaging Profile

Figure 4. Modified FLIP probe to measure UES

A pilot study was conducted on a 43 year old male with a history of lateral medullary stroke and moderate pharyngeal dysphagia. The adapted FLIP probe was inserted transnasally and location of the balloon on the distal end of the probe was confirmed fluoroscopically to be in the UES region.

Results

The balloon was distended in the UES (3ml, 10ml, 15ml volumes) without any airway compromise (see Figure 5). Narrowest diameter of the UES was obtained at baseline and during a head turn maneuvre during an 8ml distension (see Figure 6).

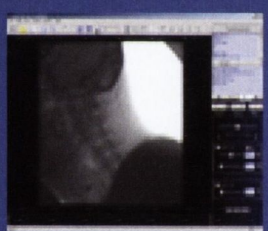


Figure 5. FLIP probe distended in UES

Figure 6. Effect of Head Turn Posture on UES Diameter

Conclusion

A new evaluation which can accurately and reliably measure the patency of the UES is required.

This preliminary study indicates that an adapted FLIP probe can be positioned safely and distended in the UES. It can provide clinically useful information regarding UES function and strategies used to improve function. Further study is required to refine this technique and to establish normative data regarding meaningful FLIP measurements and UES function.

References

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

Mellow + BP, Pandolfino JE, Lee D, Kwiatek P, Dodds AW, Gregersen H. A new technique for evaluating primary function in visceral organs: Application of the functional lumen imaging probe (FLIP) for the evaluation of the esophagogastric junction. *Physiological Measurement* 26 (5): 833-843, 2005.

Mellow + BP, Jain, B., Pandolfino J. & Gregersen, H. Do we really understand the role of the esophagogastric junction in disease? *World Journal of Gastroenterology*. 2008; 14 (30): 4822-832.

Current Evaluation of the Upper Oesophageal Sphincter (UOS) in Neurogenic Dysphagia- An International SLT Survey

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1. Background

Impaired UOS opening during swallowing is prevalent in senescent and neurological populations (e.g. PD, stroke)

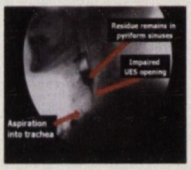


Figure 1. Videofluoroscopy image of impaired UOS opening

Current UOS evaluations are subjective and unreliable, leading to clinical uncertainty regarding candidacy for and efficacy of dysphagia interventions

2. Study Aims

a) to ascertain satisfaction amongst SLT's with current methods available to assess UOS opening during swallowing

b) to determine if SLT's would consider the Functional Lumen Imaging Profile (FLIP), a novel evaluation based on impedance planimetry, to be of benefit to dysphagia assessment

3. Methods

A 30-item online survey was disseminated to SLT professional bodies and to dysphagia Special Interest Groups.

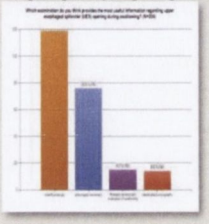
485 SLTs began survey → 254 SLTs (52.4%) completed the survey → 30 responses excluded (no dysphagia caseload) → 224 responses included in the data analysis

Table 1. Survey Participant Demographics (N=224)

		N	%			N	%
Country	Ireland	62	27.7	Work Setting	Acute hospital	147	65.6
	UK	63	28.1		Rehab setting	23	10.3
	USA	69	30.8		Community Care	40	17.9
	Europe	9	4		3rd level Ed.	8	3.6
	Canada	11	4.9		Private practice	6	2.7
	Australia	6	2.7				
	New Zealand	4	1.8				
Clinical Experience (yrs)	1-5	51	22.9	Caseload	Adults	170	75.9
	6-10	57	25.6		Paediatrics	22	9.8
	11-15	49	22		Both	32	14.3
	16-20	27	12.1				
	>20	39	17.5				
SLT Staff Position	Basic Grade	34	15.9	Dysphagia caseload	0-19%	20	8.9
	Senior Grade	88	40		20-39%	17	7.6
	Clinical Specialist	68	30.9		40-59%	41	18.3
	Research SLT	10	4.5		60-79%	74	33
	SLT Manager	18	8.2		80-100%	72	32.1

4. Results

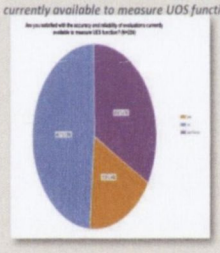
i) Which examination provides the most useful information regarding UOS opening during swallowing?



•21.4% (6/28) of SLT's with 0-19% dysphagia caseload selected PM compared to 48.6% (35/72) of SLT's with 80-100% dysphagia caseloads

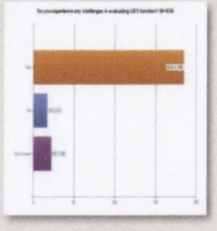
•FEES was chosen by 28.6% (8/28) of SLT's with a small dysphagia caseload (0-19%), while it was selected by just 2.8% (2/72) of those with large dysphagia caseloads (80-100%)

ii) Are you satisfied with the accuracy and reliability of evaluations currently available to measure UOS function?



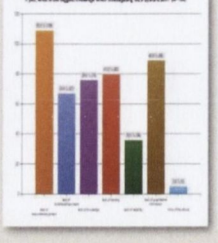
•Most satisfied with current UOS evaluation techniques were SLT's with over 20 years clinical experience (28.2%, 11/39) and SLT's working in the UK (28.6%, 18/63).

iii) Do you experience any challenges in evaluating UOS function?



•This percentage was consistent across levels of clinical experience (76.9%-86.2% range), countries (77.8%-90.3%) and work settings (65.9%-100%).

iv) If yes, what is the biggest challenge when investigating UES dysfunction?



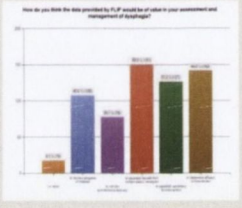
•Lack of resources/equipment was most apparent issue in SLT's with 1-5 years clinical experience (70.2%, 33/47), those working in Ireland (65.6%, 40/61) and in those working in rehabilitation settings (68.2%, 15/22).

•Lack of quantitative information from current evaluations biggest issue for SLT's working in USA (65.5%, 38/58) and in those working in acute hospital settings (51.5%, 68/132).

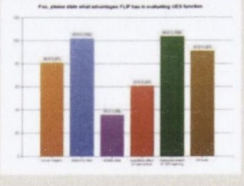
Figure 2. Functional Lumen Imaging Profile (FLIP)

FLIP is an objective evaluation tool proven to accurately and reliably measure multiple cross-sectional areas in the esophogastric junction. Pilot studies suggest FLIP can be used to measure UOS function in dysphagia

v) How do you think the data provided by FLIP would be of value in your assessment and management of dysphagia?



vi) What advantages does FLIP have in evaluating UOS function?



5. Conclusions

•Only 17.9% SLTs are satisfied with accuracy & reliability of current methods available to evaluate UOS function.

•86% SLTs experience challenges in evaluating UOS opening in patients with dysphagia

•Potential benefits to FLIP in dysphagia evaluation include objective data regarding extent of UOS opening and visual imagery of UOS.

Key References

Butler S, 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):240.

Williams R, Wallace K, Ali G, Cook I. Biomechanics of failed deglutitive upper esophageal sphincter relaxation in neurogenic dysphagia. American Journal of Physiology- Gastrointestinal and Liver Physiology. 2002;283(1):136.

Challenges in Evaluating the Upper Esophageal Sphincter in Dysphagia Practice- A Survey of SLPs

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Research Questions

(i) To ascertain satisfaction amongst SLPs with current methods available to assess upper esophageal sphincter (UES) function in patients with dysphagia

(ii) To identify any challenges currently encountered with UES evaluation.

Methodology

- 30-item survey posted to an online survey site for a three month period.
- Survey link disseminated to SLP managers in Republic of Ireland (ROI) and forwarded to two dysphagia Special Interest Groups in the United Kingdom (UK).
- Survey link posted on ASHA Division 13 discussion board in USA.
- Surveys from 224 SLPs with active dysphagia caseloads were included in data analysis (Table 1).

Table 1. Distribution of Survey Participants by Country and Work Setting (N=224)

	N	Acute Care	Rehabilitation Setting	Community Care	Third L Level Ed.	Private Practice
Republic of Ireland (ROI)	27.7%	61.3%	8.1%	27.4%	0	3.2%
United Kingdom (UK)	28.1%	68.3%	1.6%	30.2%	0	0
United States of America	30.8%	71%	15.9%	1.4%	10.1%	1.4%
Europe (outside ROI/UK)	4%	44.4%	22.2%	0	0	33.3%
Canada	4.9%	54.5%	27.3%	18.2%	0	0
Australia	2.7%	83.3%	16.7%	0	0	0
New Zealand	1.8%	50%	0	25%	25%	0
Total	224	65.6%	10.3%	17.9%	3.6%	2.7%

Results

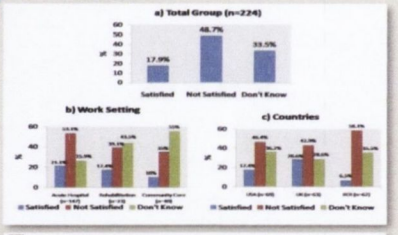

Figure 1. Satisfaction Amongst SLPs with Current UES Evaluation

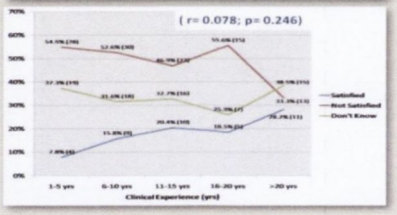

Figure 2. Satisfaction with Current UES Evaluation According to Clinical Experience (r=0.078; p=0.246)

Table 2. Challenges encountered by SLPs in Evaluating UES Function according to Work Setting and Country (195/224)

	Lack of resources	Lack of MDT	Lack of knowledge	Lack of Training	Lack of reliability	Lack of quantitative information
Total Group	55.9%	34.4%	39%	41%	18.5%	45.6%
Acute Hospital (N=132)	48.5%	31.8%	37.9%	38.6%	22%	51.5%
Rehabilitation (N=22)	68.2%	36.4%	31.8%	40.9%	9.1	45.5%
Community care (N=31)	71%	38.7%	51.6%	48.4%	12.9%	22.6%
Republic Of Ireland (N=61)	65.6%	36.1%	37.7%	42.6%	16.4%	37.7%
United Kingdom (N=49)	46.9%	30.6%	51%	40.8%	22.4%	42.9%
United States of America (N=58)	43.1%	39.7%	31%	32.8%	19%	65.5%

Table 3. Availability of UES Evaluations amongst SLPs

Availability of UES Evaluations	Total Yes N=224	Work Settings Acute N=147	Rehab N=23	Comm N=40	Countries USA N=69	UK N=63	ROI N=62
VFS	78.9%	92.5%	82.6%	27.5%	97.1%	81%	59.7%
FEES	48.1%	61.9%	26.1%	2.6%	65.7%	47.6 %	27.3%
Pharyngeal Manometry	13.9%	28%	4.5%	0%	22.4%	8.9%	9.4%
Needle EMG	5.7%	7.4%	4.5%	0%	13.8%	1.9%	0%

Conclusions

- Great dissatisfaction with current UES evaluation amongst SLPs surveyed.

- Challenges in UES evaluation include:
  1. lack of resources/equipment
  2. limited quantitative measurement of the UES
  3. inadequate knowledge and training
  4. lack of multidisciplinary input

- Given the significant impact of suboptimal UES evaluation on management of the individual with dysphagia, challenges identified by SLPs must be addressed.

This work was funded by the Health Research Board in Ireland under Grant No. HPF/2009/59

Distensibility Testing using the Functional Lumen Imaging Probe to Measure Duration and Extent of UES Opening - Preliminary Data

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4. Medical Physics and Bioengineering, Adelaide and Meath Hospital, Dublin, 24 Ireland.

Background

The Functional Lumen Imaging Profile (FLIP) is an objective evaluation tool based on principles of impedance planimetry.

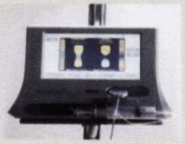


Image 1. FLIP

Image 2 FLIP Balloon

FLIP has been proven to accurately measure multiple cross-sectional areas (CSA's) in the esophogastric junction, laporoscopic lumens, the sphincter of Oddi and the ano-rectal region.

Authors hypothesise that the FLIP probe can be employed to evaluate extent and duration of UES opening during swallowing.

Methodology

Two pilot studies were conducted under videofluoroscopy on two individuals with neurogenic dysphagia

FLIP probe was inserted trans-nasally and location of the balloon on the distal end of the probe was confirmed fluoroscopically to be in the UES region. Four distensions (10ml, 20ml, 30ml & 35ml volumes) were carried out without any airway compromise.

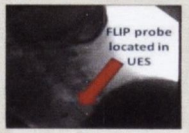
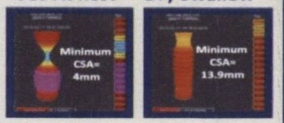


Image 3. FLIP location on videofluoroscopy

Results

Image 4. Pilot 1

UES At Rest Dry Swallow



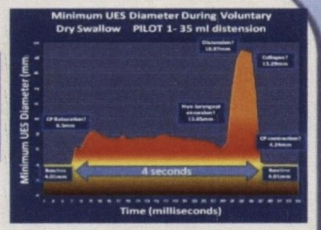


Image 5. Pilot 2

UES At Rest Dry Swallow

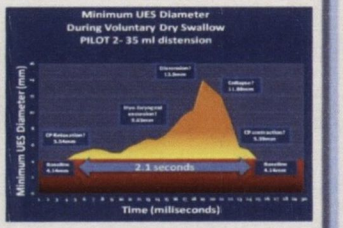
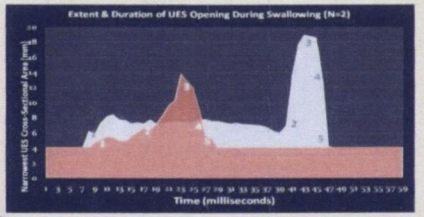


Image 6. Phases of UES Opening During Swallowing



Phases of UES Opening During Swallowing (Jacob et al, 1989)

1. CP relaxation
2. Hyo-laryngeal Excursion
1. Bolus Distension
2. Lumen Collapse
3. CP contraction

Conclusions

Preliminary studies indicate that the FLIP probe can be positioned and distended safely in the UES

FLIP can provide objective and clinically useful information regarding extent and duration of UES opening during swallowing.

The various phases of UES opening initially reported by Jacob et al (1989) may be identified from graphical representations of narrowest UES CSA data during swallowing.

Further study is currently being conducted using FLIP to obtain normative data regarding UES dynamics in healthy adults.

Key References

McMahon, BP, Jobe, B., Pandolfino, J. & Gregersen, H. Do we really understand the role of the esophagogastric junction in disease? *World Journal of Gastroenterology.* 2009: 14; 15(2): 144–150.

McMahon BP, Frøkjær JB, Liao D, Kunwald P, Drewes AM, Gregersen H. A new technique for evaluating sphincter function in visceral organs: Application of the functional lumen imaging probe (FLIP) for the evaluation of the esophago-gastric junction. *Physiological Measurement* 26 (5): 823-836, 2005.

This work was funded by the Health Research Board in Ireland under Grant No. HPF/2009/39

A Novel Distensibility Technique for Measuring Upper Esophageal Sphincter Function- Pilot Data

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Background

Impaired opening of the upper esophageal sphincter (UES) prevents food and drinks from being transported safely and efficiently from the pharynx into the esophagus during swallowing.

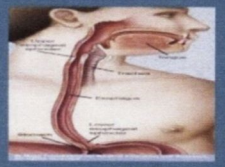

Image 1. UES

The Functional Lumen Imaging Profile (FLIP) is an objective evaluation tool based on principles of impedance planimetry.

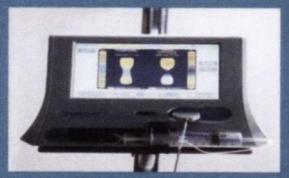

Image 2. FLIP

FLIP has been proven to accurately measure multiple cross-sectional areas (CSA's) in the esophogastric junction, and has since been employed to evaluate other anatomical sites including laporoscopic lumens, the sphincter of Oddi and the ano-rectal region.

Authors hypothesise that the FLIP probe can be employed to evaluate UES function.

Methodology

Two initial pilot studies were conducted under videofluoroscopy on two individuals with neurogenic dysphagia

Image 3. FLIP Balloon

FLIP probe was inserted trans-nasally and location of the balloon on the distal end of the probe was confirmed fluoroscopically to be in the UES region.

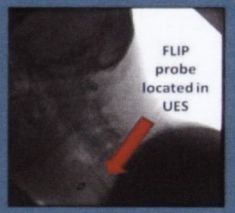

Image 4. FLIP location on Videofluoroscopy

Four distensions (10ml, 20ml, 30ml & 35ml volumes) were carried out without any airway compromise. Sixteen CSA measurements were obtained at rest and during voluntary manoeuvres.

Narrowest CSA measurement of the UES was obtained at baseline and during manoeuvres at 35 ml balloon volume.

Results

Image 5. FLIP 35ml Distensions *At Rest*

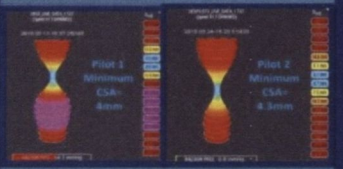

Image 6. FLIP 35ml Distensions *During Voluntary Swallow*

Table 1. Pressure and Cross-Sectional Data Across Manoeuvres

Balloon Volume	Manoeuvre /Posture	Minimum CSA (mm)		Pressure (mmHg)	
		Pilot 1	Pilot 2	Pilot 1	Pilot 2
35 ml	At rest	4	4.3	54.1	0.8
35 ml	Head turn to right	4.2	6.2	51	-9.4
35 ml	Head turn to left	4.2	-	34.5	-
35 ml	Chin down	4.2	-	69.4	-
35ml	Voluntary swallow	13.9	17.7	43.4	26.5
35ml	Phonation	4.1	5.3	47.5	-10.7

Conclusions

Preliminary studies indicate that the FLIP probe can be positioned and distended safely in the UES

FLIP can provide novel and clinically useful information regarding UES function. It can provide objective data regarding extent of UES opening at rest and during voluntary manoeuvres

Further study is currently being conducted using FLIP to obtain normative data regarding UES dynamics in healthy adults.

Key References

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Distensibility of the Upper Esophageal Sphincter in Healthy Subjects using EndoFLIP®

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Study Aims

To quantify upper esophageal sphincter (UES) distensibility in healthy subjects using EndoFLIP®, a novel distensibility tool.

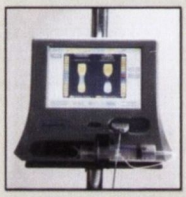

Figure 1. EndoFLIP® system

Methodology

14 healthy subjects (20-50 years) were recruited. The EndoFLIP® probe was passed orally and the balloon on the distal end of the probe was positioned across the UES (Figure 2). The protocol for distension testing can be viewed in Figure 3.

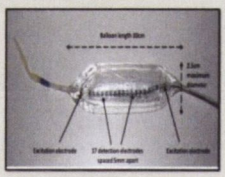

Figure 2. EndoFLIP® balloon for UES distensibility testing

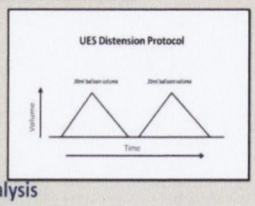

Figure 3. Study Protocol

Data Analysis

Data from 2nd distension was used. Median intra-balloon pressure (mmHg) and UOS cross-sectional area (mm2) measures and inter-quartile ranges were determined at 1, 5, 10, 15 & 20ml balloon volumes across subjects.

Kruskal-wallis tests were used. Where significance was found, multiple comparisons were made using Wilcoxin rank sum test. Bonferroni correction was made and post-hoc tests were significant at adjusted alpha level of 0.0127.

Results

13/14 subjects tolerated the study protocol (Figure 4). The geometric profile of the UES region was visible on the EndoFLIP screen across all subjects at 20ml balloon volume (Figure 5).

Figure 4. EndoFLIP® Balloon distended in UES of healthy subjects

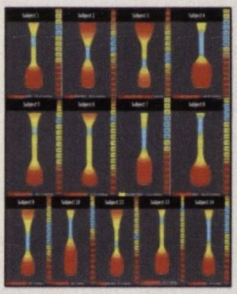

Figure 5. Geometric Profile of UES at 20ml Balloon Volume across Subjects

During distensibility testing, UES CSA ($p<.001$) and IBP ($p<.001$) altered significantly. Changes in UES CSA and IBP at specific balloon volumes are detailed in Figure 6.

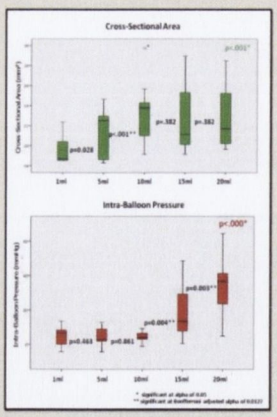

Figure 6. Changes in UES CSA and IBP between Balloon Volumes during Distensibility Testing

Conclusions

UES distensibility was evaluated for the first time in a group of adult healthy subjects using EndoFLIP®.

UES CSA increased significantly between 1ml and 5ml ($p=0.028$) and from 5ml to 10ml ($p<.001$) balloon volumes, from which point the UES resisted further distension. IBP increased significantly from 10ml to 15ml ($p=0.004$) and from 15ml to 20ml balloon volumes ($p=0.003$). These findings indicate adequate UES tone in this group.

Quantitative data derived from EndoFLIP® provide novel and clinical valuable information pertaining to UES function. Studies to investigate different patterns of UES distensibility in both elderly and clinical populations are underway.

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Regan J, McMahon BP. T1907 A Novel Distensibility Technique for Measuring Upper Esophageal Function- Pilot Data. Gastroenterology. 2010;138(5):S-604-S-

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APPENDIX 10. Peer-Reviewed Papers

1. Regan J, Walshe M, Murphy A, McMahon BP, Coughlan T. Botulinum toxin for upper oesophageal sphincter dysfunction in neurological swallowing disorders (Protocol). Cochrane Database of Systematic Reviews 2012, Issue 7. Art. No.: CD009968. DOI: 10.1002/14651858.CD009968. Copyright license number: 2951851441248
2. Regan, J., Walshe, M., Rommel, N. and McMahon, B. P. (2013), A new evaluation of the upper esophageal sphincter using the functional lumen imaging probe: a preliminary report. Diseases of the Esophagus. 26 (2): 117-123. Copyright license number: 2951851076317
3. Regan, J., Walshe, M., Rommel, N., Tack, J. & McMahon, B. New measures of upper esophageal sphincter distensibility and opening patterns during swallowing in healthy subjects using EndoFLIP®. Neurogastroenterology & Motility. 2013 (25) 1: 25-34.
4. Regan, J., Walshe, M. and McMahon, B. P. (2012), Current evaluation of upper oesophageal sphincter opening in dysphagia practice: an international SLT survey. International Journal of Language & Communication Disorders, 47 (2): 156–165. Copyright license number: 2951850287437

Botulinum toxin for upper oesophageal sphincter dysfunction in neurological swallowing disorders (Protocol)

Regan J, Walshe M, Murphy A, McMahon BP, Coughlan T

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane protocol, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2012, Issue 7

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[Intervention Protocol]

Botulinum toxin for upper oesophageal sphincter dysfunction in neurological swallowing disorders

Julie Regan[1], Margaret Walshe[2], Anne Murphy[3], Barry P McMahon[4], Tara Coughlan[5]

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Editorial group: Cochrane Upper Gastrointestinal and Pancreatic Diseases Group.
Publication status and date: New, published in Issue 7, 2012.

Citation: Regan J, Walshe M, Murphy A, McMahon BP, Coughlan T. Botulinum toxin for upper oesophageal sphincter dysfunction in neurological swallowing disorders. *Cochrane Database of Systematic Reviews* 2012, Issue 7. Art. No.: CD009968. DOI: 10.1002/14651858.CD009968.

ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

1. To establish the efficacy and safety of botulinum toxin aimed at improving UOS dysfunction in people with non progressive and progressive neurological disease.

2. To provide the best evidence to inform clinical practice.

3. To assist with future research planning.

BACKGROUND

Description of the condition

The upper oesophageal sphincter (UOS) or pharyngo-oesophageal segment (POS) is defined physiologically as a high-pressure zone forming a barrier between the pharynx and the oesophagus. This obstruction prevents diversion of air into the oesophagus during inspiration. It also protects the airway from any retrograde passage of material refluxed from the oesophagus or stomach (Singh 2005). Three muscles contribute to form the UOS: the cricopharyngeus (CP) muscle; the most inferior muscle fibres of the inferior pharyngeal constrictor muscle; and the most superior portion of the longitudinal oesophageal muscular fibres (Sivarao 2000). First described by Valsalva in 1717, the cricopharyngeus is the main component of the UOS. Arising from the lateral borders of the cricoid lamina, it is a C-shaped muscle which forms a sling around the wall of the superior aspect of the cervical oesophagus (Sivarao 2000). At rest, the sphincter has a slit-like configuration, with the CP making up the lateral and posterior walls and the cricoid lamina positioned anteriorly. The CP is bordered superiorly by the inferior constrictor muscle and merges inferiorly with the muscular layers of the cervical oesophagus. While the UOS is normally in a tonic state of contraction, it relaxes intermittently to allow transsphincteric flow of fluid or gas during antegrade (e.g. swallowing) and retrograde (e.g. emesis or belching) events (Cook 2000).

In order for the swallow to be safe and efficient, the UOS needs to open adequately to allow material to pass from the pharynx into the oesophagus. Adequate UOS opening is critical to safe and efficient swallowing due to the close proximity between the UOS and the airway entrance. Manofluoroscopic studies have demonstrated that UOS opening occurs by a combination of CP relaxation, anterior and superior hyolaryngeal excursion and bolus pressure (Cook 1989). In the initial *relaxation* phase, there is vagal inhibition of the tonic contraction of the CP muscle, as observed by needle electromyography (EMG) (Ertekin 2002). This precedes UOS opening by 200 milliseconds and lasts 300 to 600 milliseconds. In the second phase; UOS *opening* occurs via the biomechanics of hyolaryngeal excursion (Cook 1989). Suprahyoid muscles (geniohyoid, mylohyoid, stylohyoid, hyoglossus and the anterior belly of the digastric) contract, causing the hyoid bone to be pulled both anteriorly and superiorly. This movement, paired with contraction of the thyrohyoid, an infrahyoid muscle which is the main connection between the hyoid bone and the larynx, pulls the laryngeal complex in a superior and anterior direction. As the UOS is connected to the laryngeal complex via CP muscle attachment to the cricoid cartilage, the anterior portion of the UOS is pulled open. The UOS assumes an oval cross section and is raised 2 to 2.5 cm in an orad direction. In the third *distension* phase, pressure applied by the weight and volume of the onrushing bolus distends the lumen of the UOS. This distension *collapses* in the fourth phase as the bolus passes through the sphincter. Finally, in the fifth phase the UOS *closes* as the cricopharyngeus actively contracts (Cook 1989).

UOS dysfunction during swallowing has been reported in numerous acute and progressive neurological conditions including, but not limited to, brainstem stroke (Bian 2009), motor neuron disease (Higo 2002), Parkinson's disease (Restivo 2002), myasthenia gravis (Colton-Hudson 2002) and inclusion body myositis (Oh 2008). The prevalence of UOS dysfunction in people with neurological dysphagia (difficulty swallowing) varies in the literature, as rates depend on the definitions of UOS used, the heterogeneity in neurological populations studied and evaluation methods employed. For example, the reported prevalence for UOS dysfunction in people with Parkinson's disease varies from 21% (Ali 1996) to 43% (Higo 2001) and in stroke from 15% (Steinhagen 2009) to 44% (Bian 2009). Diagnosis of UOS dysfunction cannot be made from a clinical swallow examination as sensitivity and specificity of symptoms in predicting UOS dysfunction are extremely poor. Videofluoroscopy, Fibreoptic Endoscopic Evaluation of Swallowing (FEES), manometry (Butler 2009) and EMG (Ertekin 2002) are the most commonly employed instrumental evaluations to evaluate UOS function for swallowing. The cause of impaired UOS opening varies across neurological conditions and can result from disordered neurally-mediated CP muscle relaxation, suboptimal anterior and superior hyolaryngeal excursion, weak bolus propulsion, cricopharyngeal fibrosis or a combination of these factors (Cook 2000). Dysphagia frequently results which is characterised by the prevention of material passing safely and efficiently from the pharynx into the oesophagus during swallowing. Solid food can pose particular problems and can lead to choking and multiple swallowing. This typically leads to aspiration (passage of material into the trachea beyond the level of the true vocal cords) post swallow and pharyngeal retention of material. Clinical complications include aspiration pneumonia, weight loss, dehydration, malnutrition, tube feeding and increased mortality (Martino 2005; Smithard 1996). Quality of life is also frequently affected (Leow 2010).

Management of impaired UOS opening during swallowing varies across individuals and intervention can be compensatory, rehabilitative or surgical in nature. Frequently, it involves a combination of these methods. Compensation includes use of postural strategies (e.g. head turn, chin tuck) (McCulloch 2010) and voluntary manoeuvres (e.g. effortful swallow) (Hiss 2005), which are employed clinically to improve and prolong UOS opening, hence minimising aspiration and facilitating bolus clearance during swallowing. Rehabilitation programs designed to target impaired UOS opening during swallowing include the Shaker "head lifting" exercises (Shaker 1997; Shaker 2002) and the Mendelsohn manoeuvre (Kahrilas 1991). The Shaker exercises are isokinetic and isometric head lifting manoeuvres designed to strengthen suprahyoid (i.e. mylohyoid, geniohyoid, stylohyoid and anterior belly of digastric) and infrahyoid muscles (i.e. thyrohyoid), which pull open the UOS during swallowing. The Mendelsohn manoeuvre involves

purposeful prolongation of the anterio-superior displacement of the larynx at mid swallow. In cases where patients have demonstrated little or no benefit from a trial period of rehabilitation, among other factors, they may be considered for surgical or pharmaceutical interventions to optimise UOS opening. Surgical approaches employed to treat UOS dysfunction comprise cricopharyngeal myotomy (Kelly 2000; Kos 2010) or upper oesophageal dilatation (Hatlebakk 1998; Hu 2010). Pharmacological treatment consists of botulinum toxin injections into the CP muscle to improve UOS opening during swallowing (Alberty 2000; Alfonso 2010; Krause 2008; Moerman 2006).

Description of the intervention

Schneider 1994 initially described the use of Botulinum Toxin A (BTA) for the treatment of CP dysphagia. This resulted in a temporary relaxation of the CP musculature and improved opening of the UOS during swallowing. Seventy per cent of participants had more efficient bolus transport into the oesophagus during swallowing and reduced aspiration events. The intervention usually brings improvement in deglutition but most patients require reinjection in three to five months (Krause 2008). Also, side effects include inadvertent injection outside the cricopharyngeus which may result in temporary paralysis of the laryngeal musculature, causing dysphonia and, rarely, aspiration. In cases where there is uncertainty regarding the diagnosis of impaired UOS dysphagia, a positive response to a trial of botulin toxin treatment can suggest candidacy for cricopharyngeal myotomy (Krause 2008).

Since this initial study, cricopharyngeal BTA injection has been reported in over 200 patients with dysphagia of varying aetiologies with success rates between 43% and 100% (Alberty 2000; Alfonso 2010; Krause 2008). However, studies have recruited heterogeneous diagnostic groups and candidacy criteria for BTA injections vary considerably across studies. Additionally, BTA brand and dosage (2.5 to 50 units Botox®; 60-360 units Dysport®); injection site and technique (rigid endoscopy, flexible endoscopy, transcervical with EMG, transcervical CT-guided) and outcome measure evaluations (videofluoroscopy, manometry, electromyography), among other factors, have differed across studies. This has led to confusion regarding the usefulness of this technique.

How the intervention might work

BTA is a neurotoxin that inhibits presynaptic acetylcholine release and hence chemically denervates the motor endplate. Once injected, BTA binds rapidly to presynaptic cholinergic nerve terminals, impairing the release of acetylcholine (chemical denervation) at the neuromuscular junction. This results in a temporary dose-related weakness or reversible palsy of the innervated muscle. Therapeutic effects are usually seen with three days of the injection. Peripheral neuronal sprouting prevents the effects of BTA from being permanent. Reports to date suggest that effects last from two to up to six months. BTA has been used effectively in the past for the management of a number of hyperkinetic disorders (e.g. blepharospasm, torticollis, spasmodic dysphonia) with good results and limited side effects (Jankovic 1991). In more recent times, its use has expanded to treat UOS dysfunction in neurogenic dysphagia (Alberty 2000, Alfonso 2010, Bian 2009; Parameswaran 2002; Restivo 2002; Zaninnotto 2004). However, several aspects of these studies vary and its usefulness remains unclear.

Why it is important to do this review

Clinicians working with people with dysphagia secondary to UOS dysfunction as a result of acute or progressive neurological disease have difficulty determining the efficacy of BTA injections to treat dysphagia in individuals with neurogenic dysphagia. The optimum sites for injection, the optimum dosage, the method of delivery (endoscopic or transcutaneous), and the length of time before effects wear off are as yet undetermined. There are currently no systematic reviews examining the efficacy of botulinum toxin to treat UOS dysfunction in acute or progressive neurological populations, despite it being a topical issue. Given the fact that botulinum toxin is being used clinically to treat UOS dysfunction with limited evidence base, as well as the adverse events associated with the intervention, a systematic review of the evidence is required in this area. Evidence is required not only from a clinical perspective, but also to identify specific direction for future clinical trials and intervention studies in the area.

OBJECTIVES

1. To establish the efficacy and safety of botulinum toxin aimed at improving UOS dysfunction in people with non progressive and progressive neurological disease.
2. To provide the best evidence to inform clinical practice.
3. To assist with future research planning.

METHODS

Criteria for considering studies for this review

Types of studies

Only randomised controlled trials (RCTs) will be included in the review. A RCT is defined as an experiment in which an intervention (e.g. botulinum toxin) and one control treatment or no treatment are compared by being randomly allocated to participants.

In most trials one intervention is assigned to each individual but sometimes assignment is to defined groups of individuals or interventions are assigned within individuals (for example, in different orders or to different parts of the body)
We will not apply any language limits on published studies or date restrictions on trials.

Types of participants

We will include all trials involving adults (18 years +) both male and female with oro-pharyngeal dysphagia secondary to acute (e.g. stroke, traumatic brain injury (TBI) and progressive neurological disease (e.g. Parkinsons disease, motor neuron disease, multiple sclerosis). We will exclude trials that include participants with congenital neurological conditions (e.g. cerebral palsy) as dysphagia in these diagnostic groups is multifactorial.
We will exclude trials that include participants with independent or co-morbid non-neurological causes of dysphagia (i.e. head and neck cancer, tracheostomy, oesophageal disease, structural abnormality such as pharyngeal or oesophageal diverticulum).

Types of interventions

We will consider all trials that involve delivery of botulinum toxin injections into the upper oesophageal sphincter either endoscopically or transcutaneously. We will include trials that involve all dosages and types (i.e. all commercial brands) of botulinum toxin. We will consider reports of trials that include all injection sites within the UOS. We will include studies which combine botulinum toxin injections with other dysphagia interventions that are provided in the intervention group, as long as all methods except for botulinum toxin injections are provided to both treatment and control groups and the specific effects of the botulinum toxin can be reliably determined.

Comparisons

- Botulinum toxin versus no intervention
- Botulinum toxin versus placebo
- Botulinum toxin versus other intervention (i.e. traditional dysphagia rehabilitation)
- Botulinum toxin and traditional rehabilitation approach versus traditional rehabilitation approach (where traditional rehabilitation is identical in both groups)

Types of outcome measures

Binary outcomes will be reported for all primary and secondary outcomes.

Primary outcomes

1. Positive change to oral intake status (Yes/No).
2. Reduction or elimination of aspiration or laryngeal penetration on food and/or fluids as rated on objective assessment (videofluoroscopy, fibreoptic examination of swallowing safety (FEES) (Yes/No).
3. Adverse events including increase in swallowing problems, compromised medical health, negative psychological consequences, negative social consequences, hospitalisation, death (Yes/No).
4. Client and/or carer satisfaction with intervention (Yes/No).

Secondary outcomes

1. Reduction or elimination of residue in the valleculae and/or pyriform sinus/ post swallow (Yes/No).
2. Positive change in quality of life (Yes/No).

Regarding follow up of intervention effects, three time frames will be considered: immediate (> one month), medium term (one to six months) and long term (> six months). Three time points will be included to ensure that the long-lasting effects of botulinum toxin are captured.

Search methods for identification of studies

Electronic searches

We will search the following bibliographic databases for published trials:

- The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* (last update) (Appendix 1);
- Ovid MEDLINE (1950 to 2011) (Appendix 2);
- Elsevier EMBASE (1980 to 2011) (Appendix 3);
- EBSCO AMED (Allied and Complementary Medicine) 1941 to 2011 (Appendix 4);
- EBSCO CINAHL (Cumulative Index to Nursing and Allied Health Literature) 1937 to 2011 (Appendix 5).

We will also search major clinical trials registers:

- CCT (http://www.controlled-trials.com);
- Clinical Trials (http://www.clinicaltrials.gov);
- Chinese Clinical Trial Register (www.chictr.org);
- ACTR (http://www.actr.org.au/).

The search strategy has been developed for Ovid MEDLINE and translated for use on CENTRAL, EMBASE, AMED and CINAHL databases. We will search for articles with combinations of subject headings and key words relating to Botulinum toxin A; and upper oesophageal sphincter; and dysphagia or deglutition or swallowing. We will not apply language limits and will use the Cochrane Highly Sensitive Search Strategy for identifying randomised controlled trials in Ovid MEDLINE.

Searching other resources

We will scan the reference lists from all included studies to identify further relevant trials. We will handsearch published abstracts of conference proceedings from both the Dysphagia Research Society and also the European Society of Swallowing Disorders (both published in *Dysphagia*). Digestive Disease Week (published in *Gastroenterology*) will also be handsearched. Additionally, we will search ProQuest Dissertations & Theses for dissertation abstracts.

Data collection and analysis

Selection of studies

Two review authors (JR and MW) will independently inspect titles, abstracts and key words identified from the literature search. Duplicate items will be removed. The results of the literature search will be categorised as 'potentially relevant', 'relevant 'and 'not relevant'. If it is unclear from titles and abstracts whether a study should be included, then we will obtain copies of trials for further identification. We will resolve any disagreement on selection of studies by consensus discussion. We shall list those studies excluded in the 'Characteristics of excluded studies' table.

Data extraction and management

A data extraction form (Appendix 6) will be used to extract data from each potentially relevant report. This form will be used to collate study characteristics, patient details, interventions, comparisons, outcomes, eligibility for inclusion or reasons for exclusion, etc for all included studies. Two review authors (JR and MW) will independently extract details of all included studies. We will, where practicable, contact study authors for incomplete details or missing data. A third review author will extract data from a random sample of 20% of included studies. We will resolve all disagreements through discussion. All data will be entered into RevMan 5.1 (RevMan 2011).

Assessment of risk of bias in included studies

Two review authors will independently assess risk of bias in each included study. We shall describe each study in a 'Risk of bias' table and address the following issues which may be associated with biased estimates of treatment effect: sequence generation, allocation sequence concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting and other potential threats to validity (Higgins 2011).

Pre-specified questions about the adequacy of the study in relation to the above six specific domains will be answered. A judgement of 'Low' will indicate low risk of bias, whereas 'High' will indicate high risk of bias and 'Unclear' will indicate unclear or unknown risk of bias. We will use consensus to resolve disagreements and consult a third review author if disagreements still persist.

Measures of treatment effect

If sufficient trials are available and their populations are clinically similar, we will carry out meta-analyses of primary and secondary end points. We will use risk ratio (RR) and 95% confidence intervals (CI) for the analysis of dichotomous outcomes, and mean difference (MD) or standardized mean differences (SMD) and 95% confidence intervals (CI) for continuous outcomes.

Unit of analysis issues

To make sure the analysis matches the level of randomisation, we will identify the numerous variations on the designs of included studies (simple parallel group design, cluster-randomised trial, repeated measurements, recurring events, etc). As this is a review of a surgical procedure we will include both cluster-randomised and individually-randomised trials. If cluster-randomised trials are included and data have been analysed appropriately, data will be analysed by the Generic Inverse Variance method. Where the same patient is included more than once only the first episode of treatment will be included and if patients have been allowed to cross over into the other arm, the data will be analysed strictly by intention-to-treat (ITT) analysis. We will contact original authors whenever necessary. We will seek input from the Cochrane Upper Gastrointestinal and Pancreatic Diseases Group editorial base for analysis issues involving any included trials with multiple treatment groups, and cluster-randomised designs.

Dealing with missing data

In the event of missing data, we will contact the original trial authors to obtain same or to seek clarification. Alternatively, we will perform a sensitivity analysis and address the potential impact of missing data on the findings of the review in the 'Discussion' section, as recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Assessment of heterogeneity

Heterogeneity tests will be performed using a standard Chi^2 test (significance at $P < 0.1$) or an I^2 statistic ($> 75\%$). If there is evidence of heterogeneity, we will explore which factor causes it and will perform subgroup analysis according to the possible reasons.

Assessment of reporting biases

Reporting biases (publication bias, time lag bias, duplicate publication bias, location bias, citation bias, language bias or outcome-reporting bias) will be identified and minimised through a comprehensive search for studies, inclusion of unpublished studies and

use of trial registries. Reporting bias will be evaluated using funnel plot asymmetry testing, if necessary.

Data synthesis

A meta-analysis will be performed for all randomised trials included in the review. We will consider all the outcomes listed for data synthesis, and choose a random-effects model for the primary analysis, then use the fixed-effect model as a sensitivity analysis to check that results are robust regardless of which method is chosen.

Subgroup analysis and investigation of heterogeneity

We will conduct a subgroup analysis focusing on the following:

- endoscopic versus transcutaneous botulinum toxin injections;
- site of injections;
- needle used;
- botox type;
- dosage of botox.

If substantial heterogeneity (Chi² test P< 0.1 or an I^2 >50%) exists between studies for the primary outcome (i.e. aspiration/penetration and oral intake), we shall explore the reasons for heterogeneity; such as dysphagia severity, age and neurological diagnosis.

Sensitivity analysis

We will undertake sensitivity analysis to explore the potential influences on effect size. If heterogeneity results from low quality trials, we will exclude the lowest quality trials from this review.

ACKNOWLEDGEMENTS

The authors wish to thank AJ Eckardt and S Rhodes as well as the anonymous referees for their valuable advice during the preparation of this protocol.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. CENTRAL search strategy

1. (deglutition adj5 (disturbance$ or disorder$ or difficult$ or dysfunction$ or impair$ or condition$ or abnormal$ or damage$ or injur$)).mp.
2. dysphagia.mp.
3. (swallowing adj5 (disturbance$ or disorder$ or difficult$ or dysfunction$ or impair$ or condition$ or abnormal$ or damage$ or injur$)).mp.
4. deglutition/
5. deglutition disorders/
6. esophageal motility disorders/ or esophageal achalasia/ or esophageal spasm, diffuse/
7. swallow$.ti,ab.
8. or/1-7
9. pharyngeal muscles/ or esophageal sphincter, upper/
10. cricopharyn$.tw.
11. (uos or ues).tw.
12. esophagus/pp
13. cp muscle.mp.
14. or/9-13
15. exp Botulinum Toxins/
16. (botulin$ adj2 tox$).mp.
17. dyspor$.mp.
18. boto$.mp.
19. btx.ab,ti.
20. (bont adj1 a).ab.
21. oculinu$.tw.
22. Neuromuscular Agents/
23. or/15-22
24. (8 or 14) and 23

Appendix 2. MEDLINE search strategy

1. randomized controlled trial.pt.
2. randomi*ed.ab.
3. randomi*ed.ti.
4. drug therapy.fs.
5. randomly.ab.
6. trial.ab.
7. groups.ab.
8. or/1-7
9. exp animals/ not humans.sh.
10. 8 not 9
11. (deglutition adj5 (disturbance$ or disorder$ or difficult$ or dysfunction$ or impair$ or condition$ or abnormal$ or damage$ or injur$)).mp.
12. dysphagia.mp.
13. (swallowing adj5 (disturbance$ or disorder$ or difficult$ or dysfunction$ or impair$ or condition$ or abnormal$ or damage$ or injur$)).mp.
14. deglutition/
15. deglutition disorders/
16. esophageal motility disorders/ or esophageal achalasia/ or esophageal spasm, diffuse/
17. swallow$.ti,ab.
18. or/11-17
19. pharyngeal muscles/ or esophageal sphincter, upper/
20. cricopharyn$.tw.
21. (uos or ues).tw.
22. esophagus/pp
23. cp muscle.mp.
24. or/19-23
25. exp Botulinum Toxins/
26. (botulin$ adj2 tox$).mp.
27. dyspor$.mp.
28. boto$.mp.
29. btx.ab,ti.
30. (bont adj1 a).ab.
31. oculinu$.tw.
32. Neuromuscular Agents/
33. or/25-32
34. 10 and (18 or 24) and 33

Appendix 3. EMBASE search strategy

1. 'Randomized controlled trial'/exp
2. 'Randomization'/exp
3. Random*:ab,ti
4. 'double-blind procedure'/exp
5. 'single-blind procedure'/exp
6. (doubl* NEAR/1 blind):ab,ti
7. (singl* NEAR/1 blind):ab,ti
8. assign*:ab,ti
9. allocat*:ab,ti
10. trial:ab
11. groups:ab
12. or/1-11

13. 'animal'/exp NOT humans.sh.
14. 12 not 13
15. (deglutition NEAR/5 (disturbance* or disorder* or difficult* or dysfunction* or impair* or condition* or abnormal* or damage* or injur*)):ab,ti
16. dysphagia/de
17. swallowing/de
18. (swallowing NEAR/5 (disturbance* or disorder* or difficult* or dysfunction* or impair* or condition* or abnormal* or damage* or injur*)):ab,ti
19. deglut*:ti,ab
20. 'esophagus motility'/de or esophagus function disorder'/de / or 'esophagus achalasia'/de or 'esophagus spasm'/de
21. swallow*:ti,ab
22. or/15-21
23. 'pharyngeal muscle'/de or 'upper esophagus sphincter'/de
24. 'cricopharyngeus muscle'/de
25. cricopharyn*:ti,ab
26. uos:ti,ab or ues:ti,ab
27. esophagus/exp AND [physiology and endocrinology]/lim
28. 'cp muscle':ab,ti
29. or/23-28
30. 'botulinum toxin'/de
31. 'botulinum toxin A'/de
32. (botulin* NEAR/2 tox*):ab,ti
33. dyspor*:ab,ti
34. boto*:ti,ab
35. btx:ab,ti.
36. (bont NEAR/1 a):ab,ti
37. oculinu*:ab,ti
38. 'Muscle relaxant agent'/de
39. or/30-38
40. 14 and (22 or 29) and 39

Appendix 4. AMED search strategy

31. 8 and (15 or 21) and 30
30. or/22-29
29. (DE "Neuromuscular Agents")
28. TX oculinu
27. AB (bont N1 a)
26. TX btx
25. TX boto*
24. TX dyspor*
23. TX (botulin* N2 tox*)
22. (DE "Botulinum Toxins")
21. or/16-20
20. TX 'cp muscle'
19. (DE "esophagus")
18. TX uos or TX ues
17. TX cricopharyn*
16. (DE "pharynx")
15. or/9-14
14. TX swallow*
13. (DE "deglutition disorders")

12. (DE "deglutition")
11. TX (swallowing N5 (disturbance* or disorder* or difficult* or dysfunction* or impair* or condition* or abnormal* or damage* or injur*))
10. TX dysphagia
9. TX (deglutition N5 (disturbance* or disorder* or difficult* or dysfunction* or impair* or condition* or abnormal* or damage* or injur*))
8. or/1-7
7. AB trial
6. TX randomly
5. TX 'random?ed'
4. (DE "Single blind method)
3. (DE "Double blind method)
2. (DE "Random allocation)
1. (DE "Randomized controlled trials)

Appendix 5. CINAHL search strategy

39. 15 and (23 or 29) and 38
38. or/30-37
37. (MH "Neuromuscular Agents")
36. TX oculinu*
35. AB (bont N1 a)
34. TX btx
33. TX boto*
32. TX dyspor*
31. TX botulin* N2 tox*
30. (MH "Botulinum Toxins")
29. or/24-28
28. TX 'cp muscle'
27. (MH "esophagus/pp")
26. TX uos or TX ues
25. TX cricopharyn*
24 (MH "pharyngeal muscles")
23. or/16-22
22. TX swallow*
21. (MH "esophageal motility disorders") or (MH "esophageal achalasia")
20. (MH *deglutition disorders")
19. (MH "deglutition")
18. TX (swallowing N5 (disturbance* or disorder* or difficult* or dysfunction* or impair* or condition* or abnormal* or damage* or injur*))
17. TX dysphagia
16. TX (deglutition N5 (disturbance* or disorder* or difficult* or dysfunction* or impair* or condition* or abnormal* or damage* or injur*))
15. 13 not 14
14. (MH "animals+") not (MH "humans")
13. or/1-12
12. AB groups
11. AB trial
10. AB randomly
9. AB placebo
8. TI "randomi*ed"
7. AB "randomi*ed"

6. (MH "Triple-Blind Studies")
5. (MH "Therapeutic Trials")
4. (MH "Single-Blind Studies")
3. (MH "Intervention Trials")
2. (MH "Double-Blind Studies")
1. (MH "Randomized Controlled Trials")

Appendix 6. Data Extraction Form

Botulinum Toxin for Upper Oesophageal Sphincter Dysfunction in Neurological Swallowing Disorders- Study Selection, Quality Assessment & Data Extraction Form

Study ID:_____ **Lead author:**_____ **Reviewer Initials:**_____ **Date or review:**_____

General Study Information

First author	Year	Journal/Conference Proceedings etc	Country	Language	Single/Multicentre Trial	Study Duration

STUDY ELIGIBILITY

RCT	Relevant participants	Relevant interventions	Relevant outcomes
Yes / No / Unclear	Yes / No / Unclear	Yes / No / Unclear	Yes / No* / Unclear

*** issue relates to selective reporting - when authors may have taken measurements for particular outcomes, but not reported these within the paper(s). Reviewers should contact trialists for information on possible non-reported outcomes & reasons for exclusion from publication. Study should be listed in 'Studies awaiting assessment' until clarified. If no clarification is received after three attempts, study should then be excluded.**

Do not proceed if any of the above answers are 'No'.
If study to be included in 'Excluded studies' section of the review, record below the information to be inserted into 'Table of excluded studies'.

Participants and trial characteristics

Participant characteristics			
Participants :	**Treatment group**	**Comparison group 1**	**Comparison group 2 (N/A)**
	N=	N=	N=
Age (mean, median, range, SD):	Mean: Median: Range: SD:	Mean: Median: Range: SD:	Mean: Median: Range: SD:
Gender of participants: (numbers / %, etc)	Male N= Female N = Both N = Not clear	Male N= Female N = Both N = Not clear	Male N= Female N = Both N = Not clear
Relevant neurological conditions within groups :	1._____ N=_____ 2._____ N=_____ 3._____N=_____ 4._____N=_____	1._____ N=_____ 2._____ N=_____ 3._____N=_____ 4._____N=_____	1._____ N=_____ 2._____ N=_____ 3._____N=_____ 4._____N=_____
Can relevant neurological disease groups be extracted?	Yes No Unclear/to contact authors	Yes No Unclear/to contact authors	Yes No Unclear/to contact authors
Co-morbidities within exclusion criteria present/ reported? (e.g. H&N Ca, tracheostomy, congenital neuro condition, oesophageal disease, structural abnormality)			

Trial characteristics			
	Treatment group	**Comparison group 1**	**Comparison group 2 (N/A)**

(*Continued*)

Interventions: a) botulinum toxin injections b) placebo intervention c) dysphagia rehabilitation (describe nature & intensity) d) other	a)b)c)d)	a) b) c) d)	a) b) c) d)
How was participant eligibility defined?			
Type/brand of drug treatment(s) used?			
Dosage of drug treatment?			
Method used to identify injection site ?			
Injection methods (i.e. transcutaneous or endoscopic?)			
Site of injection?			
Size and calibre of needle			
Injection administered by:			
Time points of measurement collected?			
Time-frames considered: Immediate change (e.g. within one week) Medium change (1-6 months) Long term change (>6 months)	Yes/ no/ unclear Yes/ no/ unclear Yes/ no/ unclear	Yes/ no/ unclear Yes/ no/ unclear Yes/ no/ unclear	Yes/ no/ unclear Yes/ no/ unclear Yes/ no/ unclear
Trial design (e.g. parallel / cross-over*)			

Methodological quality

STUDY DESIGN	Treatment Group		Comparison Group 1		Comparison group 2...N/A	
Selection bias:						
· Sequence generation	Adequate/Inadequate/Unclear		Adequate/Inadequate/Unclear		Adequate/Inadequate/Unclear	
· Allocation concealment	Adequate/Inadequate/Unclear		Adequate/Inadequate/Unclear		Adequate/Inadequate/Unclear	
Performance Bias	Yes/No/Unclear		Yes/No/Unclear		Yes/No/Unclear	
· Blinding of participants	Yes/No/Unclear		Yes/No/Unclear		Yes/No/Unclear	
· Blinding of other personnel						
Detection Bias						
· Use of outcome measure(s) apparent	Yes/No/Unclear		Yes/No/Unclear		Yes/No/Unclear	
· Blinding of outcome assessors	Yes/No/Unclear		Yes/No/Unclear		Yes/No/Unclear	
Reporting Bias						
· Time lag to publication	Yes/No/Unclear		Yes/No/Unclear		Yes/No/Unclear	
· Language *(Please state)*	---------- Yes/No/Unclear		---------- Yes/No/Unclear		---------- Yes/No/Unclear	
· Duplicate publication	Yes/No/Unclear		Yes/No/Unclear		Yes/No/Unclear	
· Citation reporting	Yes/No/Unclear		Yes/No/Unclear		Yes/No/Unclear	
· Outcome reporting						
Attrition Bias						
· Incomplete outcome data	Yes/No/Unclear		Yes/No/Unclear		Yes/No/Unclear	
· Reasons specified	Yes/No/Unclear		Yes/No/Unclear		Yes/No/Unclear	
Intention to Treat	All participants entering trial	15% or fewer excluded	More than 15% excluded	Not analysed as 'intention-to-treat'	Unclear	Were withdrawals described? Yes Š

(*Continued*)

					No Š not clear Š	No Š

Data extraction

Outcomes relevant to your review			
	Treatment group	**Comparison group 1**	**Comparison group 2 (N/A)**
Positive change to oral intake status	Yes/No	Yes/No	Yes/No
Reduction or elimination of aspiration or laryngeal penetration on food and/or fluids as rated on objective assessment (videofluoroscopy, FEES)	Yes/No	Yes/No	Yes/No
Adverse events including increase in swallowing problems, compromised medical health, negative psychological consequences, negative social consequences, hospitalisation, death	Yes/No	Yes/No	Yes/No
Client and/or carer satisfaction with intervention	Yes / No	Yes / Nor	Yes / No
Reduction or elimination of residue in the valleculae and/or pyriform sinus/ post swallow	Yes/No	Yes/No	Yes/No
Change in quality of life	Yes/No	Yes/No	Yes/No

Other information which you feel is relevant to the results	**Other information which you feel is relevant to the results**	**Other information which you feel is relevant to the results**	**Other information which you feel is relevant to the results**	**Other information which you feel is relevant to the results**	**Other information which you feel is relevant to the results**	**Other information which you feel is relevant to the results**	**Other information which you feel is relevant to the results**
Indicate if: any data were obtained from the primary author; if results were estimated from graphs etc; or calculated by you using a formula (this should be stated and the formula given). In general if results not reported in paper(s) are obtained this should be made clear here to be cited in review	Indicate if: any data were obtained from the primary author; if results were estimated from graphs etc; or calculated by you using a formula (this should be stated and the formula given). In general if results not reported in paper(s) are obtained this should be made clear here to be cited in review	Indicate if: any data were obtained from the primary author; if results were estimated from graphs etc; or calculated by you using a formula (this should be stated and the formula given). In general if results not reported in paper(s) are obtained this should be made clear here to be cited in review	Indicate if: any data were obtained from the primary author; if results were estimated from graphs etc; or calculated by you using a formula (this should be stated and the formula given). In general if results not reported in paper(s) are obtained this should be made clear here to be cited in review	Indicate if: any data were obtained from the primary author; if results were estimated from graphs etc; or calculated by you using a formula (this should be stated and the formula given). In general if results not reported in paper(s) are obtained this should be made clear here to be cited in review	Indicate if: any data were obtained from the primary author; if results were estimated from graphs etc; or calculated by you using a formula (this should be stated and the formula given). In general if results not reported in paper(s) are obtained this should be made clear here to be cited in review	Indicate if: any data were obtained from the primary author; if results were estimated from graphs etc; or calculated by you using a formula (this should be stated and the formula given). In general if results not reported in paper(s) are obtained this should be made clear here to be cited in review	Indicate if: any data were obtained from the primary author; if results were estimated from graphs etc; or calculated by you using a formula (this should be stated and the formula given). In general if results not reported in paper(s) are obtained this should be made clear here to be cited in review

References to trial

Check other references identified in searches. If there are further references to this trial link the papers now & list below. All references to a trial should be linked under one *Study ID* in RevMan.

Code each paper	Author(s)	Journal/Conference Proceedings etc	Year
A	*The paper listed above*		
B	*Further papers*		

References to other trials

Did this report include any references to published reports or unpublished data of potentially eligible trials not already identified for this review? If yes, give list contact name and details		
First author	Journal / Conference	Year of publication

Overall Quality Score (GRADE rating)	
· **High** · **Moderate** · **Low** · **Very low**	**High** (Randomised trial /double upgraded Ix studies Further research is very unlikely to change our confidence in the estimate of effect
	Moderate: Downgraded randomised trials /Upgraded observational studies Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
	Low: Double downgraded randomised trials/Observational studies Low quality- Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
	Very Low : Triple down graded randomised trials/downgraded observational studies/case series/case reports. Any estimate of effect is very uncertain

Review Author Comments:
Signed: .....
Date: .....

HISTORY

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CONTRIBUTIONS OF AUTHORS

J Regan and M Walshe wrote protocol. A Murphy developed search strategy. B McMahon and T Coughlan reviewed protocol.

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Authors have no declaration of interest to report.

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Research Report

Current evaluation of upper oesophageal sphincter opening in dysphagia practice: an international SLT survey

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Abstract

Background: The assessment of adequate upper oesophageal sphincter (UOS) opening during swallowing is an integral component of dysphagia evaluation.
Aims: To ascertain speech and language therapists' (SLTs) satisfaction with current methods for assessing UOS function in people with dysphagia and to identify challenges encountered by SLTs with UOS evaluation.
Methods & Procedures: A survey was disseminated to 82 SLT managers in Ireland; to two dysphagia Special Interest Groups in the UK; and to the Royal College of Speech & Language Therapists' *Bulletin* periodical. A survey link was also posted on the American Speech and Hearing Association (ASHA) Division 13 (Dysphagia) web forum.
Outcomes & Results: Surveys from 224 SLTs with active dysphagia caseloads were included in data analysis. Only 17.9% (40/224) of SLTs were satisfied with the accuracy and reliability of UOS evaluations currently being employed in dysphagia practice. Satisfaction with current UOS evaluation was not associated with the level of clinical experience ($r = 0.078$; $p = 0.246$). Eighty-seven per cent (195/224) of SLTs working with dysphagia experience challenges in UOS evaluation. Challenges reported include lack of resources/equipment (55.9%), limited quantitative information (45.6%), lack of training (41%) and knowledge (39%) in UOS function, and limited multidisciplinary team involvement (34%).
Conclusions & Implications: SLTs across all levels of clinical experience are not satisfied with current UOS evaluation in dysphagia practice. Based on the specific challenges identified, recommendations to progress SLT evaluation of UOS function in people with dysphagia are proposed.

Keywords: dysphagia, upper oesophageal sphincter, evaluation, survey, speech and language therapists

What this paper adds

What is already known on this subject

The assessment of adequate UOS opening during swallowing is an integral component of dysphagia evaluation. Limitations to current UOS evaluations (i.e. videofluoroscopy, FEES, pharyngeal manometry) prevent objective and reliable measurement of the extent and duration of UOS opening. Measuring UOS opening and determining candidacy for dysphagia interventions can be challenging for SLTs working with dysphagia.

What this paper adds

Only 18% of SLTs are satisfied with current UOS evaluation in dysphagia practice. Dissatisfaction is evident internationally and across work settings, and is reported from highly specialized SLTs. Challenges encountered by SLTs with UOS evaluation include lack of resources/equipment (55.9%), limited quantitative information (45.6%), lack of training (41%) and knowledge (39%) in UOS function, and limited multidisciplinary team involvement (34%).

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Introduction

The assessment of adequate upper oesophageal sphincter (UOS) or pharyngo-oesophageal segment (PES) opening during swallowing is an integral component of dysphagia evaluation. The UOS forms a barrier between the pharynx and the oesophagus. It comprises the cricopharyngeus (CP) muscle, the inferior pharyngeal constrictor (IPC) and the most proximal cervical oesophagus (Lang and Shaker 2000). During swallowing, the UOS needs to open sufficiently to ensure food and fluids (including saliva) can pass safely and efficiently from the pharynx into the oesophagus. Five phases of UOS opening during swallowing have been observed (Cook et al. 1989). In the initial relaxation phase before the pharyngeal swallow is initiated, the CP muscle (the main muscular component of the UOS) relaxes due to vagus nerve inhibition (Ertekin and Aydogdu 2002). In the second phase, anterior and superior hyo-laryngeal excursion occurs due to contraction of suprahyoid (geniohyoid, mylohyoid, anterior belly of digastric muscle) and infrahyoid (thyrohyoid) muscles (Pearson et al. 2010, Mepani et al. 2009). The anterior attachment of the relaxed CP muscle to the cricoid cartilage causes the UOS to be stretched open upon hyo-laryngeal displacement. Of note, adequate UOS opening has been observed with hyo-laryngeal excursion and absent CP relaxation, while the reverse is not the case (Ali et al. 1996, Cook 2006). In the third distension phase, lingual and pharyngeal peristalsis increases intra-bolus pressure which further expands the UOS lumen during swallowing (Leonard et al. 2009). The UOS lumen collapses in the fourth phase as the bolus passes through the sphincter. Finally, in the fifth phase the UOS closes as the CP actively contracts post-swallow.

Impaired UOS opening during swallowing can be caused by impaired CP relaxation, reduced hyo-laryngeal excursion, poor lingual and pharyngeal pressure and is frequently caused by a combination of each of these factors (Cook 2006). UOS dysfunction is a symptom of pharyngeal dysphagia associated with numerous conditions including but not restricted to lateral medullary stroke (Bian et al. 2009), Parkinson's disease (Ertekin et al. 2002), motor neuron disease (Ertekin et al. 2000), inclusion body myositis (Oh et al. 2008) and radiation therapy post-head and neck cancer (Hu et al. 2010). When the UOS does not open adequately, material is unable to pass efficiently into the oesophagus. This frequently leads to aspiration post-swallow and can result in clinical complications such as aspiration pneumonia, weight loss, malnutrition, dehydration and decreased quality of life.

Several management strategies have been devised to improve UOS opening and hence minimize clinical complications of dysphagia. These strategies can be compensatory (e.g. head turn postures; McCulloch et al. 2010), rehabilitative (e.g. Shaker 'head-lifting' exercises; Shaker et al. 2002) or surgical (e.g. myotomy, Kos et al. 2010; dilatation, Solt et al. 2001; and botulinum toxin A injection to CP muscle, Zaninotto et al. 2004). Crucially, treatment to improve UOS opening during swallowing should be guided by the underlying cause of impaired UOS opening. Individuals with weak hyo-laryngeal excursion or poor bolus propulsion tend to respond better to dysphagia rehabilitation and are typically poor candidates for surgical interventions. Those with poor CP relaxation who do not benefit from a trial period of rehabilitation may be deemed better candidates for surgery (Ali et al. 1996, Kelly 2000). Objective and reliable diagnosis of both the cause and degree of impaired UOS opening is therefore essential in order to provide appropriate and beneficial dysphagia treatment.

Current instrumental evaluations employed to measure UOS opening in people with dysphagia present with numerous limitations which lead to confusion regarding candidacy for and efficacy of the dysphagia interventions described above. Videofluoroscopy (VFS) is criticized for being a subjective evaluation and proven to be unreliable in the detection of the presence and nature of UOS dysfunction (McCullough et al. 2001, Kuhlemeier et al. 1998, Stoeckli et al. 2003). Based on VFS alone, clinicians are unable to diagnose disordered CP relaxation and there is significant variability in the quantification of both anterior and superior hyo-laryngeal movement across research studies (Molfenter and Steele 2010). Equally, evaluation of pharyngeal pressure during swallowing from videofluoroscopy has been subjective to date (Leonard et al. 2009). Fibreoptic endoscopic evaluation of swallowing (FEES) is restricted by a 'white out period', which prevents visualization of the degree and extent of UOS opening during the swallow. Information pertaining to UOS opening and hyo-laryngeal excursion therefore needs to be inferred from location of residue post-swallow. Additionally, only the upper portion of the UOS can be observed during FEES without any view of middle or lower portions of the sphincter. Conclusions therefore cannot be made regarding complete UOS opening. Despite these limitations to VFS and FEES, a distinction between the various causes of impaired UOS opening is essential in order to provide appropriate and effective dysphagia management.

Needle-electromyography (EMG) is a neurophysiological evaluation that can be useful diagnostically to measure the timing and extent of CP relaxation during swallowing (Ertekin and Aydogdu 2002) and to evaluate contraction of individual suprahyoid muscles (e.g. geniohyoid, mylohyoid) during hyo-laryngeal

excursion (Alfonsi et al. 2010). However, needle-EMG cannot provide SLTs with a holistic measurement of UOS opening. While surface EMG is employed in rehabilitation to provide biofeedback on the amplitude and duration of isolated muscle group activity (e.g. submental-EMG to measure suprahyoid muscle group contraction during swallowing), it is not considered to be a diagnostic tool (Huckabee and Steele 2006).

Solid-state pharyngeal manometry (PM) can provide valuable quantitative measurements of the extent and duration of UOS pressure changes during swallowing (Butler et al. 2009). However, manometric pressure changes reflect alterations in UOS 'squeeze' on manometry probe sensors, and therefore provide very indirect gauges of the extent of UOS opening. Additionally, technical (e.g. sensor placement due to radial asymmetry of UOS, sensor displacement upon UOS excursion) and physiological (age, gender, emotional state) issues have complicated the development of normal UOS pressure ranges during swallowing (Butler et al. 2009). The emergence of combined video-manometric examinations help to relate pressure changes to structural movement and bolus flow.

The development of new techniques such as high-resolution manometry (HRM) and multichannel intraluminal impedance (MII) has provided new insights into normal UOS opening, the nature of pharyngeal dysphagia, and the effectiveness of compensatory and surgical interventions on UOS pressure and bolus flow (McCulloch et al. 2010, Omari et al. 2011). In settings where these evaluations are available to SLTs, these tests will address some but not all of the issues outlined above. However, reliable quantification of extent of UOS opening and the cause of impaired UOS opening continues to challenge most SLTs working with dysphagia in clinical practice.

Study objectives

Evaluation of UOS opening during swallowing is regarded as a challenge to most SLTs working with dysphagia. Despite this, no information is currently available on the perceptions of SLTs on evaluating UOS function and the obstacles encountered when evaluating UOS opening in dysphagia. The purposes of this study were (1) to ascertain satisfaction internationally amongst SLTs working with dysphagia with current methods available to assess UOS function; and (2) to establish the nature of any challenges encountered by SLTs in current UOS evaluation.

Methods

Ethical approval for the study was obtained from the Joint Ethics Committee of St. James and The Adelaide & Meath Hospitals incorporating the National Children's Hospital, Dublin. A 25-item electronic survey (10–15-min completion time) was designed and piloted with seven SLTs. The survey was refined based on feedback provided. The survey was posted on an internet-based survey site (http://www.surveymonkey.com) in May 2010 (13/25 questions relevant to this study are given in Appendix A). The survey was set to close in July 2010. Emails advertising the survey were sent to 82 SLT managers in the Republic of Ireland (ROI) for dissemination to staff. Of note, SLTs are currently trained to work with dysphagia at a postgraduate level in ROI. Responses from SLTs without active dysphagia caseloads would be excluded from the data analysis. Notice of the survey was also forwarded to two dysphagia special interest groups in the UK and information pertaining to the survey was included in an edition of the Royal College of Speech & Language Therapists' (RCSLT) *Bulletin*. A link to the survey was also posted on the Division 13 American Speech & Hearing Associations (ASHA) web forum. Descriptive statistics were used to analyse survey finding. MINITAB version 14 (Du 2005) was used to determine an association (Pearson's (r) correlation) between satisfaction with current UOS evaluation and level of clinical experience.

Results

Responses were obtained from 485 SLTs over the 3-month period. A response rate could not be determined for the following reasons:

- The survey was disseminated by SLTs in ROI and it was not possible to determine how many SLTs received the survey link. There is no national record in ROI regarding number of SLTs who have obtained postgraduate training to work in dysphagia.
- Information on the size of membership in UK dysphagia SIGs could not be obtained and thus the number of SLTs who accessed the survey.
- The number of ASHA Division 13 members using the internet web forum could not be established.

Two hundred and thirty-one (47.6%) of the responses received were incomplete and excluded from analysis leaving a total of 254 completed surveys eligible for analysis. Incomplete responses occurred as some SLTs were unable to access online video clips that formed part of the survey. Of the 254 completed responses, a further 30 were excluded as respondents did not have an active dysphagia caseload. A total of 224 surveys were suitable for analysis.

Table 1. Distribution of survey participants by country and work setting ($n = 224$) (Q3 and Q4)

	n	Acute care	Rehabilitation setting	Community care	Third-level education	Private practice
Republic of Ireland	27.7% (62)	61.3% (38)	8.1% (5)	27.4% (17)	0	3.2% (2)
UK	28.1% (63)	68.3% (43)	1.6% (1)	30.2% (19)	0	0
USA	30.8% (69)	71% (49)	15.9% (11)	1.4% (1)	10.1% (7)	1.4% (1)
Europe (outside Ireland/UK)	4% (9)	44.4% (4)	22.2% (2)	0	0	33.3% (3)
Canada	4.9% (11)	54.5% (6)	27.3% (3)	18.2% (2)	0	0
Australia	2.7% (6)	83.3% (5)	16.7% (1)	0	0	0
New Zealand	1.8% (4)	50% (2)	0	25% (1)	25% (1)	0
Total	224	65.6% (147)	10.3% (23)	17.9% (40)	3.6% (8)	2.7% (6)

In addition to establishing total group findings ($n = 224$), a sub-group analysis was performed to explore differences in satisfaction and challenges across countries (USA, $n = 69$; UK, $n = 63$; ROI, $n = 62$) and work settings (acute care, $n = 147$; rehabilitation, $n = 23$; community, care $n = 40$). Smaller subgroups (i.e. third-level education and private practice) were excluded from this analysis. Respondents were also divided according to the level of clinical experience (1–10 years, $n = 108$; > 11 years, $n = 115$). Given the wide range of clinical experience within the total response group (0 to > 20 years) as well as the large number of respondents with substantial clinical dysphagia experience, 10 years was chosen as the cut-off point to categorize SLTs according to their level of experience. This provided an opportunity to capture responses from an international highly specialist SLT group. Responses were also analysed according to dysphagia caseload (0–59%, $n = 78$; 60–100%, $n = 146$) and nature of the client group (adults, $n = 170$; paediatric/mixed, $n = 54$). Details regarding nationality and work settings of survey participants are shown in Table 1.

Satisfaction amongst SLTs with the current methods used to evaluate UOS function (Appendix A, Q11)

Only 17.9% (40/224) of SLTs surveyed were satisfied with the accuracy and reliability of evaluations currently available to measure UOS function. Forty-nine per cent of SLTs reported dissatisfaction with current UOS evaluation (Figure 1). SLTs most dissatisfied with current UOS evaluations included those working in acute hospital settings (53.1%, 78/147), those with large (60–100%) dysphagia caseloads (54.8%, 80/146), and SLTs working with adults (51.2%, 87/170). There was no significant association between satisfaction with current UOS evaluation and level of clinical experience ($r = 0.078$; $p = 0.246$) (Figure 2).

Challenges in UOS evaluation (Appendix A, Q12 and Q13)

Eighty-seven per cent (195/224) of SLTs surveyed experience challenges in evaluating UOS opening during swallowing. Challenges were more evident from SLTs working with adults (86.5%, 147/170) and from respondents with more (> 11 years) clinical experience (85.6%, 125/146). Challenges were also increased in rehabilitation settings (100%, 23/23), although highly prevalent in acute hospitals (85.7%, 126/147). The 195/224 SLTs who reported challenges in evaluating UOS dysfunction were subsequently asked to select the most prominent challenges experienced from six examples provided within the survey (Appendix A, Q13). The most frequently selected challenges reported within this group ($n = 195$) are detailed in Table 2.

Lack of resources/equipment was the most frequently reported challenge reported by SLTs when evaluating UOS impairment in people with dysphagia (56%, 109/195) (Table 2). Availability of resources/equipment used to evaluate the UOS (i.e. VFS, FEES, PM, needle EMG) is presented in Table 3a. VFS is accessible to over three-quarters of respondents (78.9%, 176/224) and to 92.5% (136/147) of SLTs working in acute hospitals. Nevertheless, VFS availability is markedly reduced in ROI (59.7%, 37/62) and is available to just over one-quarter (27.5%, 11/40) of SLTs working in community care.

FEES is available to less than half of SLTs surveyed (48.1%) (Table 3a), with low access in rehabilitation (26.1%) and, in particular, in community care settings (2.6%) (Table 3a). However, there was good access to FEES in acute care settings (62.6%) and from respondents working in the United States (65.2%). The

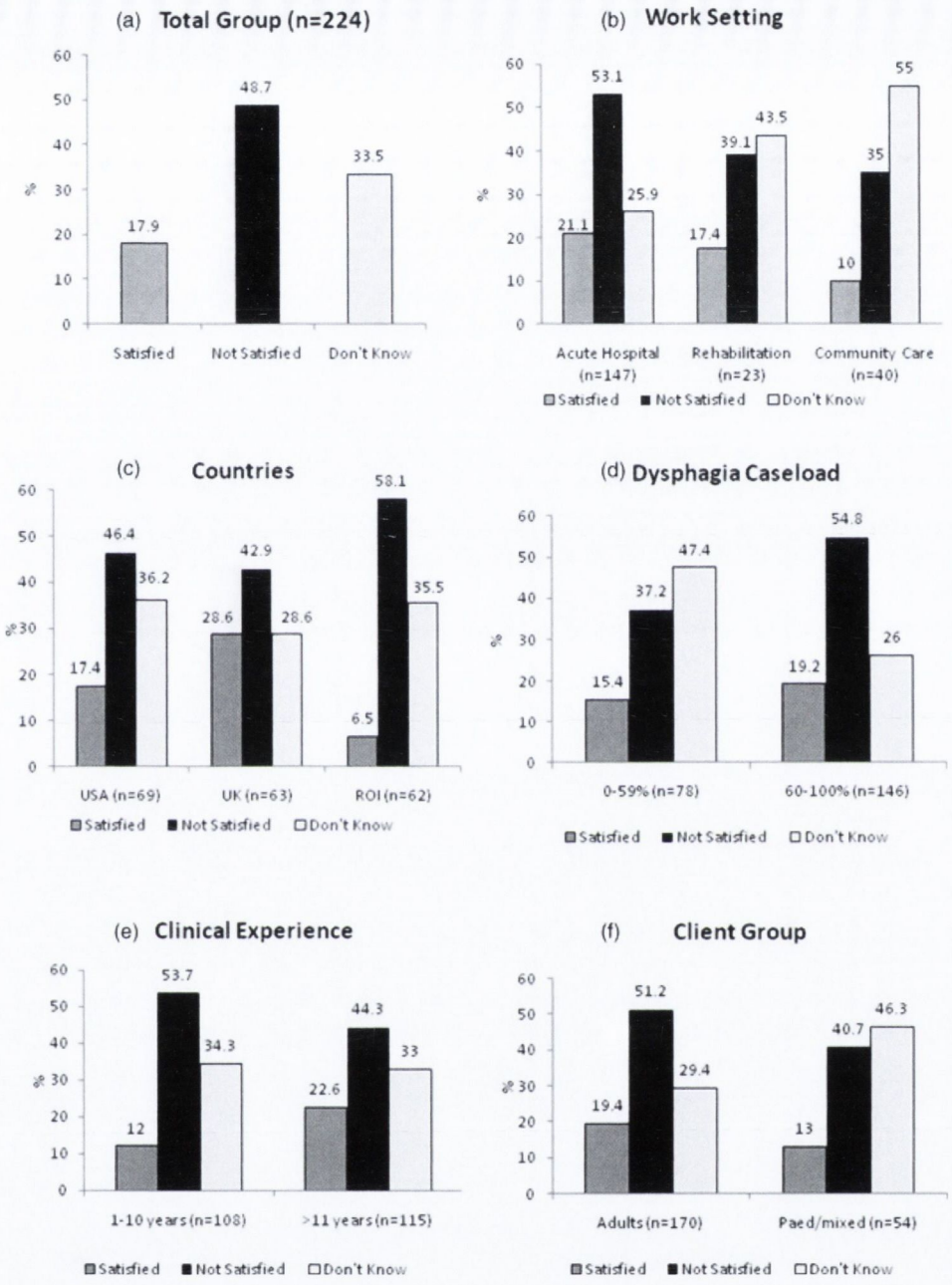

Figure 1. Satisfaction amongst SLTs with the current evaluation of UOS function (Q11).

availability of physiological dysphagia evaluations (i.e. PM, needle EMG) was low across the response group (Table 3a). PM was available to just 13.9% of SLTs, and to less than one-fifth (18%) of SLTs working in acute care (Table 3a). Just 6.0% of SLTs reported availability of needle EMG in UOS evaluation, which increased to 7.4% in acute care and to 13.6% availability in the United States (Table 3a).

The second challenge most frequently selected by SLTs was the lack of quantitative information derived from current UOS evaluations (45.6%, 89/195). This was the most commonly reported challenge for SLTs working in acute hospital settings (51.5%, 68/132) and for SLTs working in the United States (65.5%; 38/58) (Table 2). It was more evident in SLTs working with adults (48.7%, 74/152), in respondents with larger (60–100%) dysphagia caseloads (50.4%, 65/129) and by SLTs with more (> 11 years) clinical experience (57.6%, 57/99).

Forty-one per cent (80/195) of SLTs reported lack of training as a challenge in UOS evaluation. This issue was most apparent in SLTs based in community care (48.4%, 15/31) and those working in ROI (42.6%, 26/61) (Table 2). Certified training (i.e. attendance at

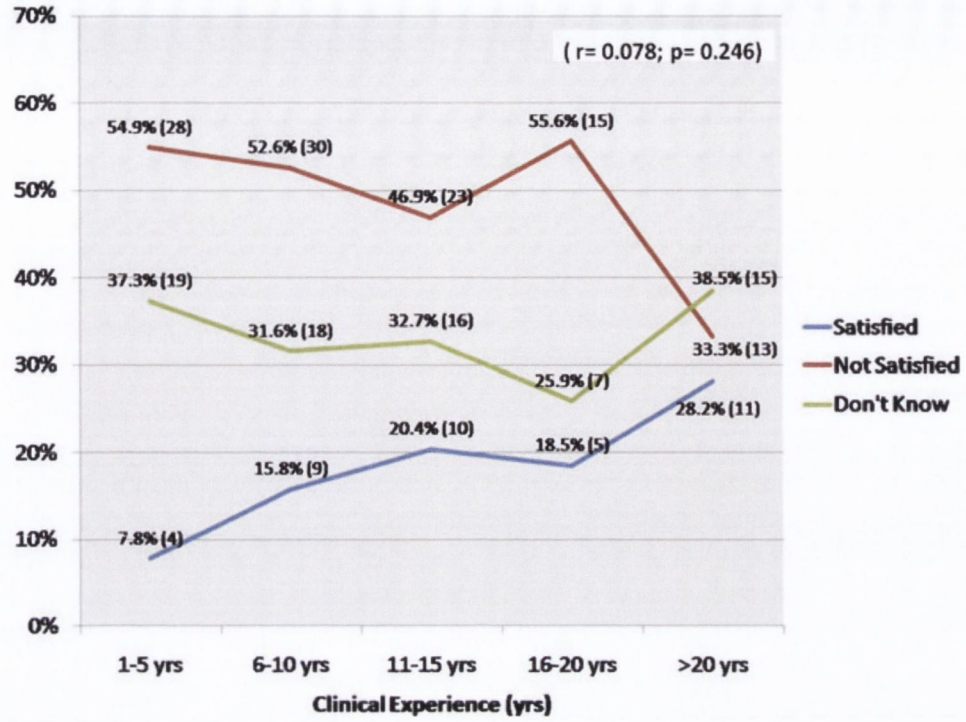

Figure 2. Satisfaction with the current UOS evaluation according to the level of clinical experience.

an accredited training workshop or course) received by SLTs in instrumental examinations (i.e. VFS, FEES, PM) is detailed in Table 3b. Of concern, certified training in VFS, FEES and PM is distinctly lower across all countries and across all work settings than levels of availability for each of these evaluations. One exception is VFS training in ROI (68.8%, 44/55), which is higher than VFS availability (59.7%, 37/62). These data suggest that SLTs are carrying out instrumental examinations without appropriate training (Table 3b).

Over one-third (39%, 76/195) of SLTs reported lack of knowledge to be a challenge in UOS evaluation. SLTs frequently reported limited focus on UOS opening as part of basic dysphagia training. Lack of knowledge regarding UOS function was particularly evident from SLTs in community care settings (51.6%, 16/31). Of note, lack of knowledge was the most common challenge reported by SLTs working in the UK (51%, 25/49). Lack of knowledge was reported by 50% (7/14) SLTs with paediatric/mixed caseloads and by 47.4% (45/99) of SLTs with less (1–10 years) clinical experience.

Lack of MDT in UOS investigation was reported as a challenge by over one-third of respondents (34.4%, 67/195). This issue was most apparent in community care settings (38.7%, 12/31), and was also frequently reported by SLTs working in the United States (39.7%, 23/58) (Table 2). Lack of reliability was selected as a challenge in evaluating UOS dysfunction by less than one-fifth of respondents (18.5%, 36/195) (Table 2). However, 22% of those working in acute care consider lack of reliability to be an issue with current UOS

Table 2. Nature of the challenges encountered by SLTs in evaluating UOS function according to work setting and country (n = 195/224) (Q13)

		Lack of resources	Lack of MDT	Lack of knowledge	Lack of Training	Lack of reliability	Lack of quantitative information
Total (n = 195)		55.9% (109)	34.4% (67)	39% (76)	41% (80)	18.5% (36)	45.6% (85)
Work setting	Acute hospital (n = 132)	48.5% (64)	31.8% (42)	37.9% (50)	38.6% (51)	22% (29)	51.5% (68)
	Rehabilitation (n = 22)	68.2% (15)	36.4% (8)	31.8% (7)	40.9% (9)	9.1 (2)	45.5% (10)
	Community care (n = 31)	71% (22)	38.7% (12)	51.6% (16)	48.4% (15)	12.9% (4)	22.6% (7)
Country	Republic of Ireland (n = 61)	65.6% (40)	36.1% (22)	37.7% (23)	42.6% (26)	16.4% (10)	37.7% (23)
	UK (n = 49)	46.9% (23)	30.6% (15)	51% (25)	40.8% (20)	22.4% (11)	42.9% (21)
	USA (n = 58)	43.1% (25)	39.7% (23)	31% (18)	32.8% (19)	19% (11)	65.5% (38)

evaluation. Reliability was also regarded as a bigger issue for SLTs with large (60–100%) dysphagia caseloads (21.7%, 28/129) and for those with more (> 11 years) clinical experience (20%, 20/99).

Discussion

SLTs internationally are dissatisfied with current methods of UOS evaluation and experience multiple challenges in assessing UOS function in people with dysphagia. This low satisfaction levels with current UOS evaluations is evident even in highly specialized clinicians and is cause for concern. If SLTs are experiencing difficulty diagnosing the presence, severity and cause of impaired UOS opening, people with dysphagia may not be receiving appropriate dysphagia treatment (Cook 2006). Completion of a similar survey on other healthcare professionals involved in the management of UOS disorders (e.g. Ear Nose and Throat surgeons) may be of interest to determine if comparable satisfaction levels are found and the same challenges are encountered.

The biggest challenges in current UOS evaluation reported by SLTs relate to resources/equipment. This is despite the fact that access to VFS and FEES was higher in this survey than in previous research (Bateman et al. 2007, Mathers-Schmidt and Kurlinski 2003). Access to equipment was reported as an issue across all countries, but most noticeably in ROI, perhaps due to the late development of dysphagia services in this country, commencing only in the 1990s. Dysphagia services in ROI are also not provided routinely in private medical care settings and rely largely on public sector funding. Interestingly, availability of resources has been reported as a challenge across all work settings, despite variation in equipment availability. In rehabilitation and particularly community care settings, routine access to a 'first port of call' instrumental evaluation of swallowing (i.e. VFS or FEES) is limited. This is not surprising given the lack of Radiology or ENT departments in these settings. Perhaps the joint development of a care pathway for referring people for VFS/FEES examinations in local acute care settings from the community/rehabilitation setting may address, at least in part, this issue.

In acute care and adult services, access to VFS and FEES are much improved but availability of physiological measurements (e.g. PM, EMG) in order to identify accurately the cause of UOS dysfunction is inconsistent. Additionally, where SLTs in acute care and adult services do have access to physiological measurements, lack of quantitative information derived from current UOS evaluations continues to pose a challenge when measuring UOS opening for swallowing. It is hoped that the adaption of gastrointestinal (GI) evaluations (e.g. HRM, MII) and their combination with VFS will address this issue of reliable quantification in UOS evaluation in the future. The development of a relatively low-cost tool with established sensitivity and specificity that is portable and not confined to acute settings would be ideal to address this gap in UOS evaluation.

Based on survey findings, challenges encountered with UOS evaluation in dysphagia practice are by no means restricted to resources/ equipment. An independent challenge frequently reported by SLTs was a lack of knowledge regarding impaired UOS opening. Numerous respondents highlighted a limited focus on normal phases of UOS opening and the various causes of impaired UOS opening as part of basic dysphagia training. SLTs queried whether impaired UOS opening can be caused by a weakness at the pharyngeal stage of swallowing (e.g. reduced hyo-laryngeal excursion). This lack of clarity is confusing SLTs regarding their role in the management of impaired UOS opening. Additionally, respondents report confusion regarding definitions such as 'UOS dysfunction', 'UOS achalasia' and 'UOS spasm', and whether these terms refer to CP relaxation alone or if they encompass the multiple potential causes of impaired UOS opening. Poor awareness of optimal treatment for varying causes of UOS impairment was also described, which has major implications for the patient with dysphagia. Specifically, SLTs were unsure regarding candidacy criteria for rehabilitation versus candidacy for referral to ENT/GI colleagues.

Knowledge gaps pertaining to UOS opening reported by SLTs may also relate to limited certified training (i.e. attendance at a postgraduate accredited training workshop or course) in instrumental assessments used to evaluate the UOS (Table 3). A marked disparity exists across all countries and work settings between access to VFS, FEES and PM and certified training to perform and analyse these evaluations (Table 3). Compulsory attendance at a certified training course in order to complete and analyse any examinations (e.g. VFS, PM) may address knowledge gaps and improve reliability of interpretation. The third area which presented as a challenge for SLTs across all work settings is lack of routine care pathways in the multidisciplinary management for patients with impaired UOS opening (Table 2). It is interesting that multidisciplinary dysphagia management is an issue which is surfacing across the USA, UK and ROI despite differences in the delivery of healthcare services. Perhaps ambiguity regarding the roles of various MDT members reflects, in part, the recent growth in the number of multidisciplinary interventions being developed and refined to treat dysphagia (Kos et al. 2010, Moerman 2006, Zaninotto et al. 2004, Belafsky 2010). SLTs report frequent confusion regarding which professional (i.e. ENT/GI surgery) to refer to for further UOS investigation. SLTs

Table 3. UOS evaluations: availability and certified training amongst SLTs (Q8)

		Work Settings			Countries			Dysphagia Caseload		Clinical experience		Client group	
	Total yes, $n = 224$	Acute, $n = 147$	Rehab, $n = 23$	Community, $n = 40$	USA, $n = 69$	UK, $n = 63$	ROI, $n = 62$	0–59%, $n = 78$	60–100%, $n = 146$	1–10 years, $n = 108$	> 11 years, $n = 115$	Adults, $n = 170$	Paediatrics/ both, $n = 54$
3a. Availability of UOS evaluations													
VFS	78.9% (176)	92.5% (136)	82.6% (19)	27.5% (11)	97.1% (66)	81% (51)	59.7% (37)	62.8% (49)	87% (127)	57% (71)	65.2% (75)	82.9% (141)	64.8% (35)
FEES	48.1% (102)	62.6% (87)	26.1% (6)	2.6% (1)	65.2% (43)	47.6% (30)	27.3% (15)	35.9% (28)	50.7% (74)	23.1% (25)	38.3% (44)	52.8% (85)	31.5% (17)
Pharyngeal manometry	13.9% (28)	18% (23)	4.5% (1)	0% (0)	25.4% (16)	8.9% (5)	9.4% (5)	9% (7)	14.4% (21)	2.8% (3)	5.2% (6)	15.3% (23)	9.3% (5)
Needle EMG[a]	5.7% (11)	7.4% (9)	4.5% (1)	0% (0)	13.6% (8)	1.9% (1)	0% (0)	5.1% (4)	4.8% (7)	1.9% (2)	16.5% (19)	6.2% (9)	3.7% (2)
3b. Certified Training[b] in UOS evaluations													
VFS	65.6% (147)	72.7% (109)	50% (12)	39.5% (17)	75.4% (52)	56.7% (38)	68.8% (44)	59% (46)	69.2% (101)	65.7% (71)	65.2% (75)	67.6% (117)	55.5% (30)
FEES	34.5% (69)	41.9% (54)	31.8% (7)	5.1% (2)	54.7% (35)	29.3% (17)	18.2% (10)	33.3% (26)	29.5% (43)	23.1% (25)	38.3% (44)	37.1% (59)	18.5% (10)
Pharyngeal Manometry	5.1% (9)	6.4% (7)	0% (0)	0% (0)	6.9% (5)	0% (0)	4.4% (2)	2.6% (2)	4.8% (7)	2.8% (3)	5.2% (6)	6.6% (9)	0% (0)

Notes: [a]Training in nEMG not surveyed as not applicable to the SLT profession.
[b]Certified training is defined as attendance at a postgraduate-accredited training workshop or course.

describe unheeded requests for UOS investigation and limited interventions for those who are reviewed by ENT/GI colleagues. The need for closer collaboration with ENT/GI colleagues was expressed by many respondents. SLTs also communicated a lack of clarity regarding the extent of their role in UOS investigation within the multidisciplinary team. SLTs also state they are unsure how much information they are expected to provide to colleagues when referring patients for further UOS investigation. This uncertainty regarding MDT roles would surely be enough independently to complicate the management of impaired UOS opening in people with dysphagia. Again, the development of explicit care pathways and referral criteria at a local level may address some of these areas of concern.

Conclusions and recommendations

This survey investigated issues within the SLT profession with current UOS investigation in people with dysphagia. While responses were largely from highly specialized clinicians, focus on less experienced clinicians and those with smaller dysphagia caseloads were also included. There is great dissatisfaction with the current evaluation of UOS opening during swallowing within the SLTs surveyed, which is not limited to less experienced clinicians. Current techniques may not be providing all the information required by SLTs in order to deliver appropriate dysphagia treatment. Lack of resources/equipment, limited quantitative measurement of the UOS, inadequate knowledge and training, and lack of multidisciplinary care are all key concerns. In order to progress UOS evaluation within the SLT profession, specific measures need to be taken. These include (1) increased emphasis on normal and abnormal UOS opening as part of basic dysphagia training to increase knowledge base; (2) improved access to and training in standard and newer GI physiological evaluations adapted to objectively evaluate UOS opening; and (3) established local multidisciplinary care pathways to diagnose accurately and appropriately manage individuals with impaired UOS opening. This study provides a starting point for examining this area.

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Appendix A: Survey

Section A: Demographic section

1. Please state your staff position (or equivalent where terminologies differ). Basic grade SLT, Senior SLT, Clinical Specialist SLT, SLT Manager, Research SLT
2. What is your clinical experience in years? 1–5, 6–10, 11–15, 16–20, > 20
3. Where are you based? Ireland, UK, Europe (outside ROI/UK), USA, Canada, Australia, NZ
4. What setting are you working in? Acute hospital, Rehabilitation setting, University/3rd Level Education, Community Care Setting, Private Practice, Other
5. What is your caseload? Adults, Paediatrics, Both
6. Do you have a dysphagia caseload? Yes, No
7. What percentage of your clinical caseload is dysphagia? 0–19%, 20–39%, 40–59%, 60–79%, 80–100%

Section B: Current evaluation of the upper oesophageal sphincter

8. Have you received certified training in the following? Videofluoroscopy, FEES, Pharyngeal manometry, Surface EMG, Other
9. Which of the following dysphagia evaluations are available at your work setting? Videofluoroscopy, FEES, Pharyngeal Manometry, Needle EMG of CP muscle
10. Which examination do you think provides the most useful information regarding upper oesophageal sphincter (UOS) opening during swallowing? Videofluoroscopy, FEES, Pharyngeal Manometry, Needle EMG
11. Are you satisfied with the accuracy and reliability of evaluations currently available to measure UOS function? Yes, No, Don't know
12. Do you experience any challenges in evaluating UOS function? Yes, No, Don't know
13. If yes, what is the biggest challenge when investigating UOS dysfunction? Lack of resources/equipment, Lack of training, Lack of multidisciplinary team, Lack of knowledge, Lack of reliability, Lack of quantitative information, None of the above

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DISEASES OF THE ESOPHAGUS

Original article

A new evaluation of the upper esophageal sphincter using the functional lumen imaging probe: a preliminary report

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SUMMARY. **Objective and reliable evaluation of upper esophageal sphincter (UES) opening during swallowing based on videofluoroscopy and pharyngeal manometry challenges dysphagia clinicians. The functional lumen imaging probe (FLIP) is a portable tool based on impedance planimetry originally designed to measure esophogastric junction compliance. It is hypothesized that FLIP can evaluate UES distensibility, and can provide UES diameter and pressure measurements at rest, during swallowing, and during voluntary maneuvers. Eleven healthy adult subjects consented to FLIP evaluation. The probe was inserted transorally, and the balloon was positioned across the UES. Two 20-mL ramp distensions were completed. Changes in UES diameter and intraballoon pressure were measured during dry and 5-mL liquid swallows, and during voluntary swallow postures and maneuvers employed in clinical practice. The protocol was completed by 10 of 11 healthy subjects. Mean intraballoon pressure increased throughout 5-mL (5.8 mmHg; –4.5–18.6 mmHg), 10-mL (8.7 mmHg; 2.3–28.5 mmHg), 15-mL (17.3 mmHg; 9.5–34.8 mmHg), and 20-mL (31.2 mmHg; 16–46.3 mmHg) balloon volumes. Mean resting UES diameter (4.9 mm) increased during dry swallows (9.2 mm) and 5-mL liquid swallows (7.7 mm). Mean UES diameter increased during 5-mL liquid swallows with head turn to right (8.1 mm) and left (8.3 mm), chin tuck (8.4 mm), effortful swallow (8.5 mm), Mendelsohn maneuver (8.1 mm), and supraglottic swallow (7.8 mm). FLIP was safely inserted and distended in the UES, and provided useful quantitative data regarding UES distensibility and UES diameter changes during swallowing maneuvers. Further research is being conducted to explore the role of FLIP in UES evaluation.**

KEY WORDS: **dysphagia, evaluation, functional lumen imaging probe, upper esophageal sphincter.**

BACKGROUND

Patterns and mechanisms of upper esophageal sphincter (UES) opening are still not fully understood. During swallowing, cricopharyngeal muscle relaxation is closely followed by anterior and superior hyolaryngeal excursion that stretches open the UES. Pressure from the on-coming bolus further distends the UES to approximately 8 mm, and then the UES closes all within 0.5 seconds (Fig. 1).[1,2] Interrater reliability of UES opening measures based on two-dimensional videofluoroscopy images is poor.[3] Currently, there is no diagnostic method capable of objectively differentiating between each phase of UES opening. A better understanding of UES function could improve the rehabilitative or surgical treatment of aspiration, and inefficient bolus clearance in individuals with dysphagia.

The functional lumen imaging probe (FLIP) is a novel distensibility evaluation technique based on the principles of impedance planimetry.[4] FLIP was first used to evaluate esophogastric junction (EGJ) distensibility and has since evaluated the upper esophagus, the sphincter of Oddi, and laparoscopic lumens.[4–8] To date, no studies have investigated the role of FLIP in evaluating UES function. Videofluoroscopy studies have demonstrated safe insertion and distension of

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Competing interests: BM previously worked as a consultant for Crospon Ltd and is currently a minor shareholder in Crospon Ltd.

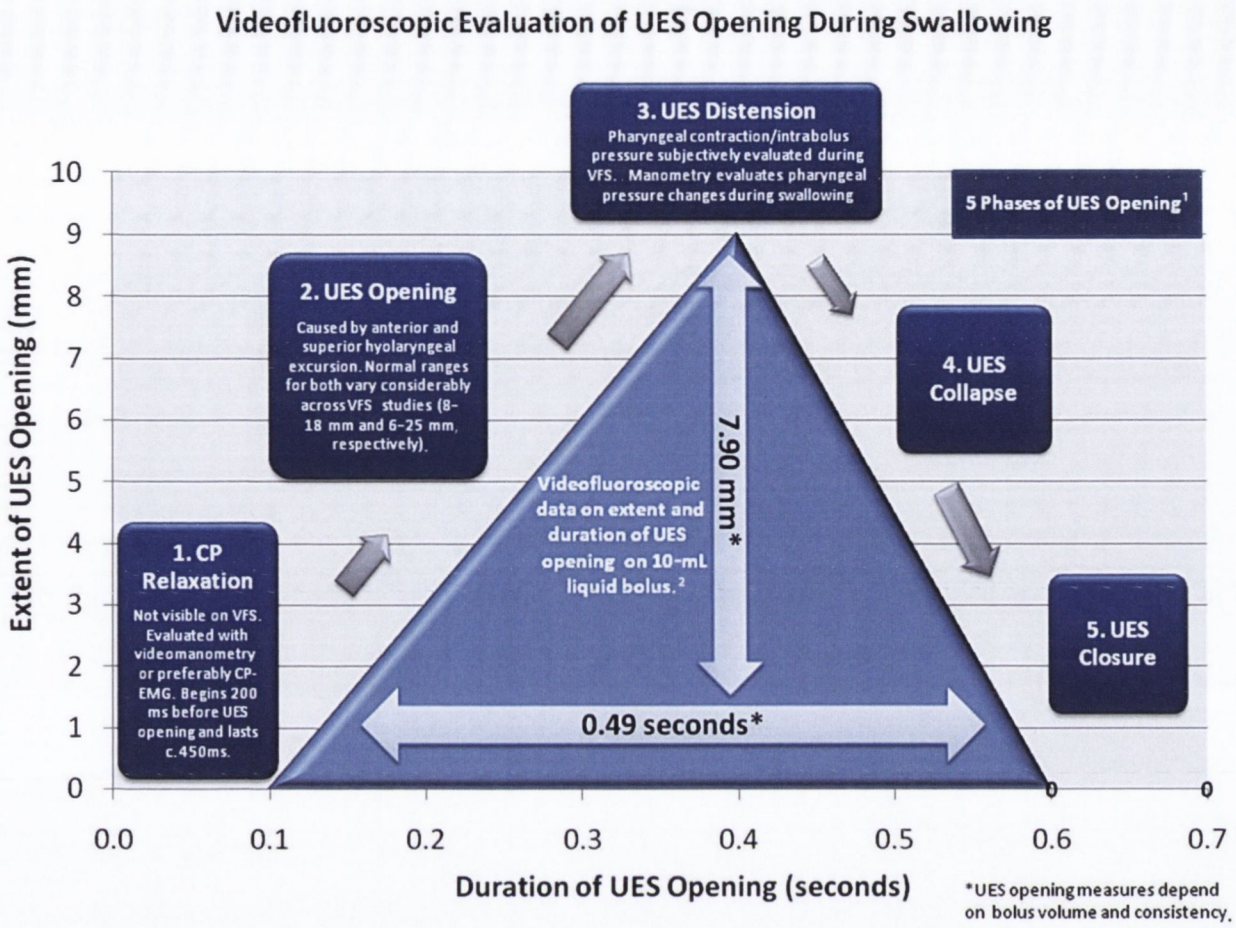

Fig. 1 Current evaluation of upper esophageal sphincter (UES) opening. CP, cricopharyngeus; CP-EMG, cricopharyngeus-electromyogaphy; VFS, videofluoroscopy.

the FLIP balloon in the UES of patients with dysphagia (Fig. 2C).[9] The aims of this exploratory study were to use FLIP (i) to derive preliminary data on UES distensibility and (ii) to measure UES diameter and intraballoon pressure at rest, during swallowing, and during voluntary maneuvers previously described in a pilot group of healthy subjects.[10]

METHODS

Subjects

Subjects were recruited from a pool of healthy volunteers. Inclusion criteria were: (i) no history of oropharyngeal or esophageal dysphagia; (ii) no history of gastrointestinal, neurological, or respiratory disease; and (iii) no history of head and neck cancer, or ear, nose, and throat conditions. Eleven healthy adults (three male), with a mean age of 34 years (range 20–50; standard deviation 11.3), met inclusion criteria. Written consent was obtained from subjects. Before each FLIP evaluation, all voluntary swallowing maneuvers included in the assessment were explained and demonstrated to subjects. Ethical approval was obtained from the Research Ethics Committee, University Hospitals Leuven, Belgium.

EndoFLIP® system

A commercially developed FLIP (EndoFLIP system, Crospon Ltd, Galway, Ireland) was used (Fig. 2A). A polyutherane balloon with a maximum volume of 60 mL was mounted on the distal 14 cm of a probe (EF-325) (length 240 cm, diameter 25 mm) attached to the EndoFLIP unit (Fig. 2B). This balloon assumes a 10-cm long cylindrical shape with a maximum diameter of 2.5 cm. The maximum balloon diameter was critical to prevent airway compromise during balloon distension. Across a 7.5-cm segment within the balloon, 17 ring electrodes were spaced 5 mm apart to obtain 16 impedance planimetry measurements (Fig. 2B). This allowed diameter and pressure changes above (i.e. pharynx) and below (i.e. upper esophagus) the UES to be captured and for UES opening to be observed despite its upward shift during swallowing. Excitation electrodes situated at either end of the 17 ring electrodes emitted a constant low electrical current within the balloon. The probe

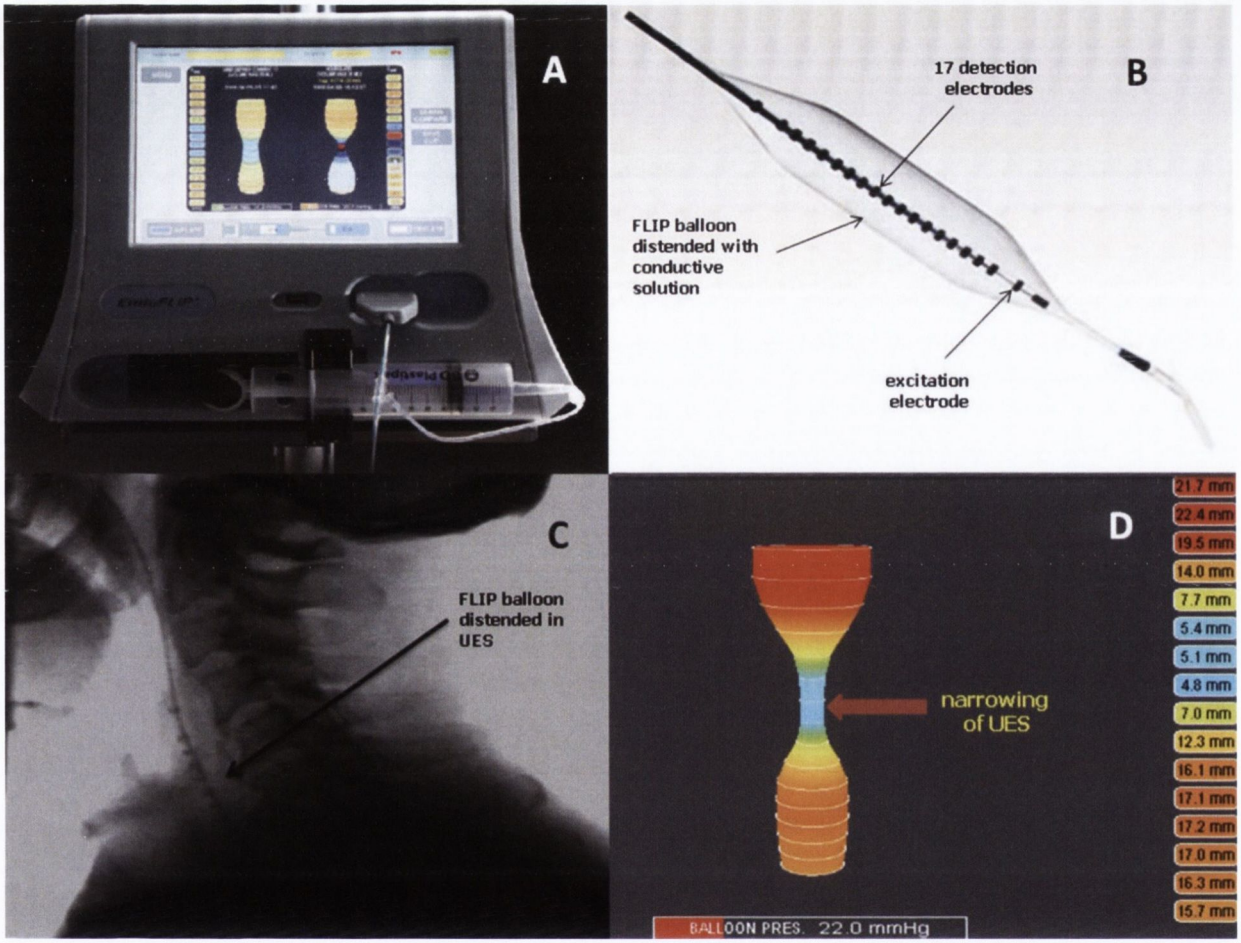

Fig. 2 EndoFLIP® system. (A) EndoFLIP. (B) Functional lumen imaging probe (FLIP) balloon. (C) FLIP balloon safely distended in upper esophageal sphincter (UES) during videofluoroscopy. (D) Geometric profile of UES on EndoFLIP screen.

also contained a solid-state pressure transducer to measure intraballoon pressure.

Protocol

The EndoFLIP system was positioned beside the subject who was seated upright on a chair within the clinic room (Neurogastroenterology and Motility Clinic, University Hospital Leuven). The equipment was powered on, and both the syringe and a pre-calibrated probe were connected to the EndoFLIP unit. An automated purge sequence initiated by the EndoFLIP removed air from the balloon. Topical anesthesia (Lignocaine spray) was administered to the posterior pharyngeal wall, and subjects were instructed to swallow. The tip of the FLIP probe was lubricated and inserted orally by a member of the research team until the balloon at the distal end of FLIP was judged to have passed into the proximal esophagus (30-cm marking on FLIP catheter). The subject was transferred to a bed and seated in a 90-degree angle upright position. The FLIP catheter was placed outside of the subjects' teeth and held by a researcher to minimize displacement during the evaluation.

When the subject was accustomed to the probe, the probe balloon within the esophagus was distended with 10-mL saline solution from the syringe using a touch-screen function on the EndoFLIP monitor. The inflated balloon was slowly retracted until the hourglass shape of the UES could be visualized on the EndoFLIP screen (17- to 20-cm marking on FLIP catheter) (Fig. 2D). This confirmed the balloon position in the UES. While holding the catheter in place, the balloon was deflated by pressing the touch-screen control on the unit monitor.

After a brief habituation period (1–2 minutes), two 20-mL ramp distensions were completed (rate 60 mL/minute). Subjects were requested not to swallow during distensions, and the EndoFLIP screen was monitored to ensure the balloon remained in position. The balloon was reinflated with either 12- or 15-mL conductive solution (balloon volume was reduced to 12 mL after two studies to optimize tolerance). Once a baseline measure of minimum UES diameter (mm) and intraballoon pressure (mmHg) was recorded, subjects were asked to complete the following:

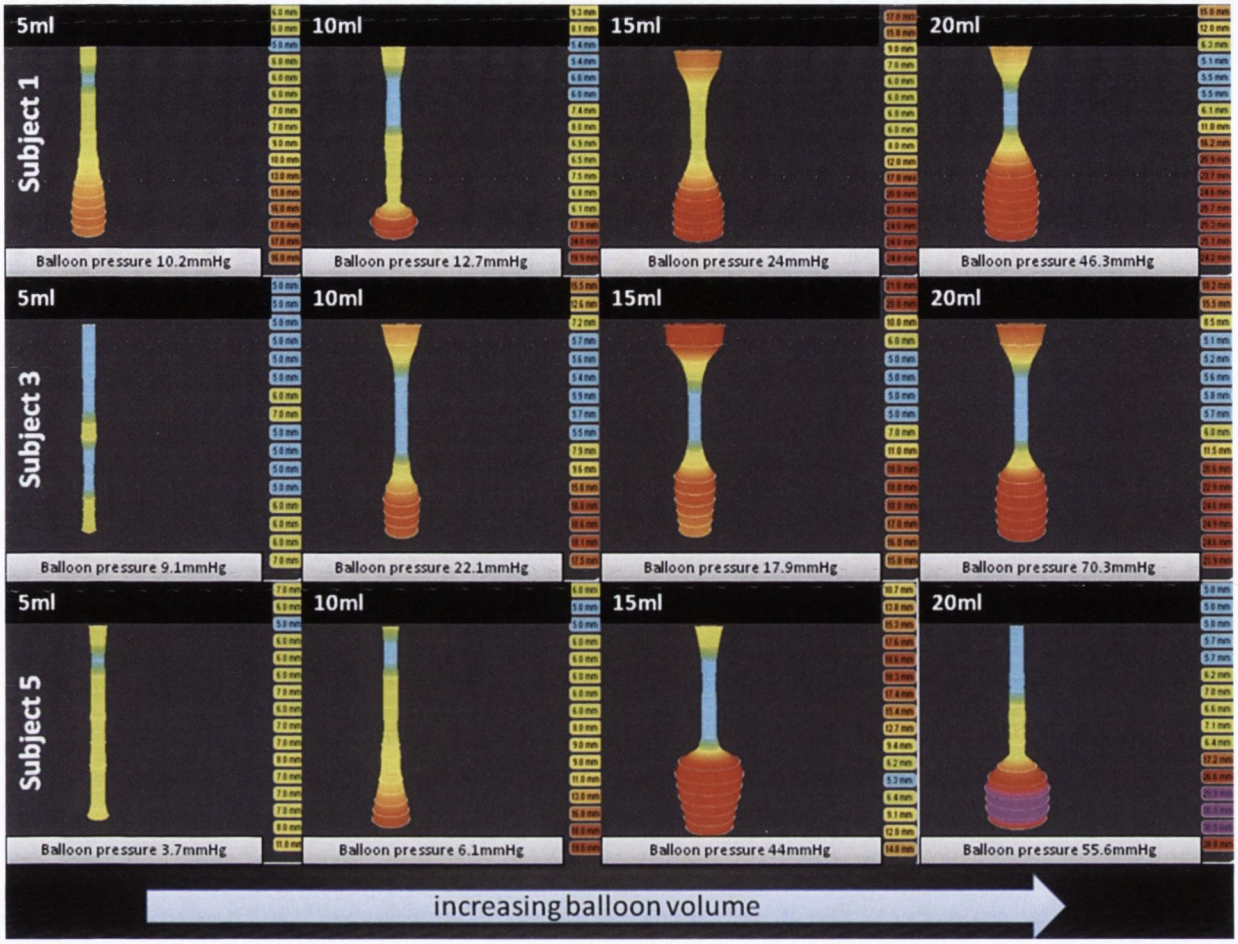

Fig. 3 Upper esophageal sphincter distensibility.

1 dry swallow
2 5-mL liquid swallow delivered orally via syringe
3 voluntary swallow maneuvers during 5-mL liquid swallows delivered orally via syringe: (i) swallow with head turn to left; (ii) swallow with head turn to right; (iii) swallow with chin tuck; (iv) effortful swallow; (v) swallow with Mendelsohn maneuver; and (vi) supraglottic swallow.

A minimum 10-second time period between the performances of each strategy was enforced to easily identify maneuvers during data analysis. The time (in seconds) displayed on the EndoFLIP device at the execution of each maneuver was recorded. When the protocol was completed, the balloon was deflated, and the probe was removed.

Data analysis

To evaluate UES distensibility, mean cross-sectional area (CSA) and intraballoon pressure measures were determined at 5-, 10-, 15-, and 20-mL volumes. Using times (in seconds) recorded from the EndoFLIP unit, measures of (i) minimum UES diameter (mm) and (ii) minimum intraballoon pressure (mmHg) were attained at baseline, during dry and liquid swallowing,

Table 1 Change in upper esophageal sphincter cross-sectional area and intraballoon pressure during 20-mL ramp distension ($n = 10$)

EndoFLIP balloon volume (mL)	Pressure (mmHg)				Cross-sectional area (mm^2)			
	Mean	SD	Minimum	Maximum	Mean	SD	Minimum	Maximum
5	5.8	7.7	–4.5	18.6	20.9	1.9	18.5	23.5
10	8.7	8.7	–3.5	28.5	22.1	2.2	19.1	25.5
15	17.3	7.9	8.8	34.8	23	2.8	19.7	28.4
20	31.2	10.2	16	46.3	23.5	2.8	20.2	28.4

SD, standard deviation.

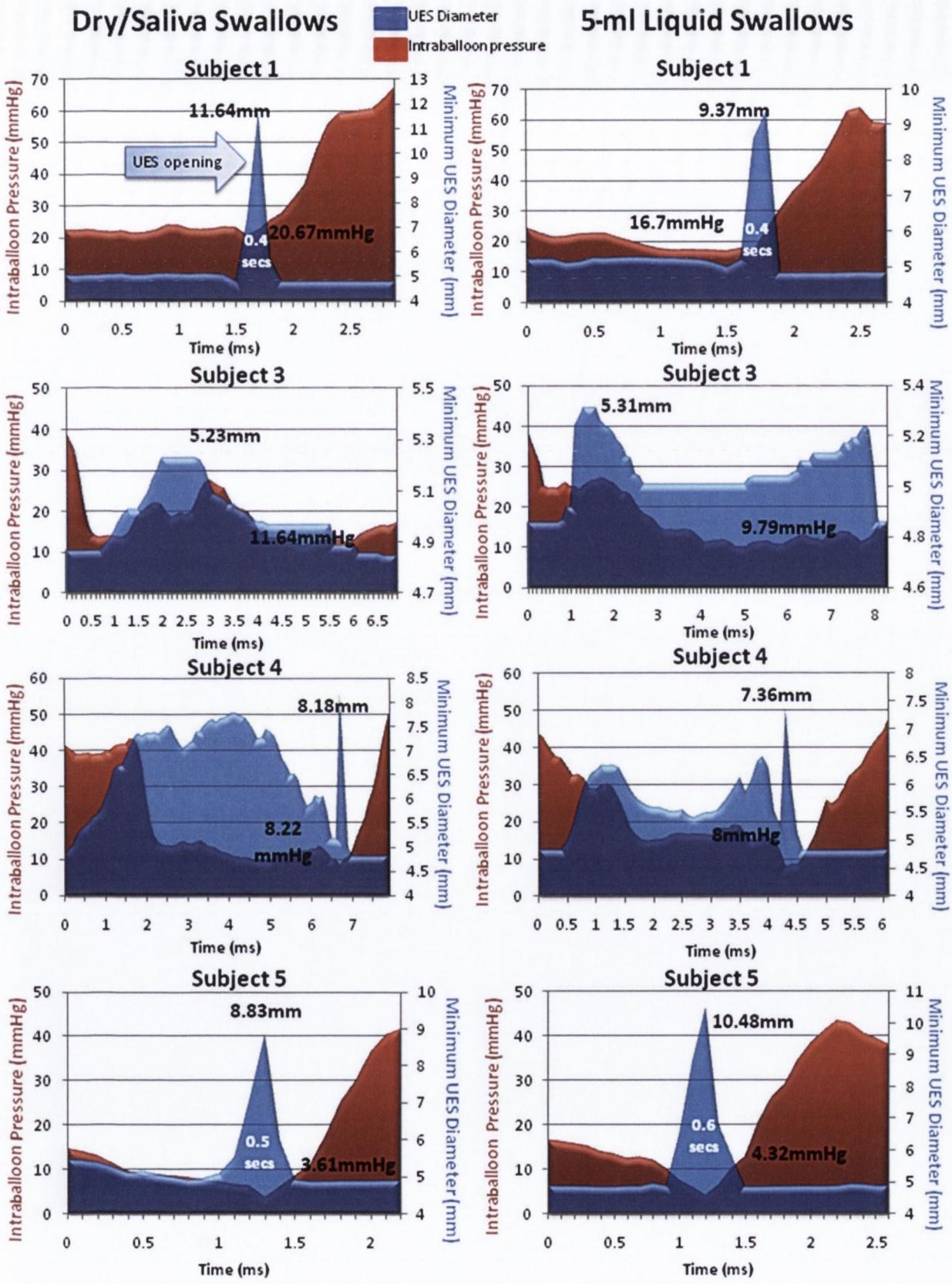

Fig. 4 Upper esophageal sphincter (UES) diameter and intraballoon pressure changes during swallowing in four healthy subjects.

Table 2 UES diameter and intraballoon pressure changes during swallowing

Maneuver		*n*	Mean minimum UES diameter (mm)	Mean minimum intraballoon pressure (mmHg)
At rest		10	4.9 mm (4.8–5, SD: 0.1)	30.2 mmHg (18.2–62.9, SD: 14.7)
Dry swallow		10	9.2 mm (5.2–11.6, SD: 2)	8.6 mmHg (3–20.7, SD: 5.3)
5 mL	Baseline	10	7.7 mm (5.3–9.4, SD: 1.1)	8 mmHg (3.6–16.7,SD: 4)
liquid	Head turn right	9	8.1 mm (5.1–15.8,SD: 3.1)	1.5 mmHg (–2.9–5.4, SD: 3.9)
swallows	Head turn left	9	8.3 mm (5.1–15.9, SD: 3.2)	4.2 mmHg (–0.4–9.6, SD: 3.7)
	Chin tuck	9	8.4 mm (4.9–12.7, SD: 2.4)	7 mmHg (4.2–12.5, SD: 3.5)
	Effortful swallow	9	8.5 mm (4.9–15.2, SD: 2.9)	3.4 mmHg (–4.7–10.8, SD: 4.7)
	Mendelsohn maneuver	9	8.1 mm (5.0–14.7, SD: 2.8)	5.2 mmHg (2.7–11.5, SD: 3.9)
	Supraglottic swallow	9	7.8 mm (5–15.2, SD: 3)	2.7 mmHg (–5.5–14.6, SD: 5.5)

SD, standard deviation; UES, upper esophageal sphincter.

and during voluntary maneuvers. Descriptive statistics were used to analyze results.

RESULTS

Ten of 11 subjects completed the study protocol. Subject 2 did not complete the study because of intolerance of the distended balloon in the UES for a prolonged period. Subject 1 did not complete voluntary postures and maneuvers during 5-mL liquid swallows, as it was only upon completion of this initial study, which authors ascertained that liquid could be swallowed with the balloon distended in the UES and then extended the protocol for subsequent studies.

During 20-mL ramp distensions, the EndoFLIP balloon assumed an hourglass shape at the level of the UES across all subjects (Fig. 3). Mean increases in intraballoon pressure and CSA during ramp distensions are detailed in Table 1.

Figure 4 demonstrates changes in mean UES diameter (mm) and intraballoon pressure (mmHg) during dry swallows and 5-mL liquid swallows.

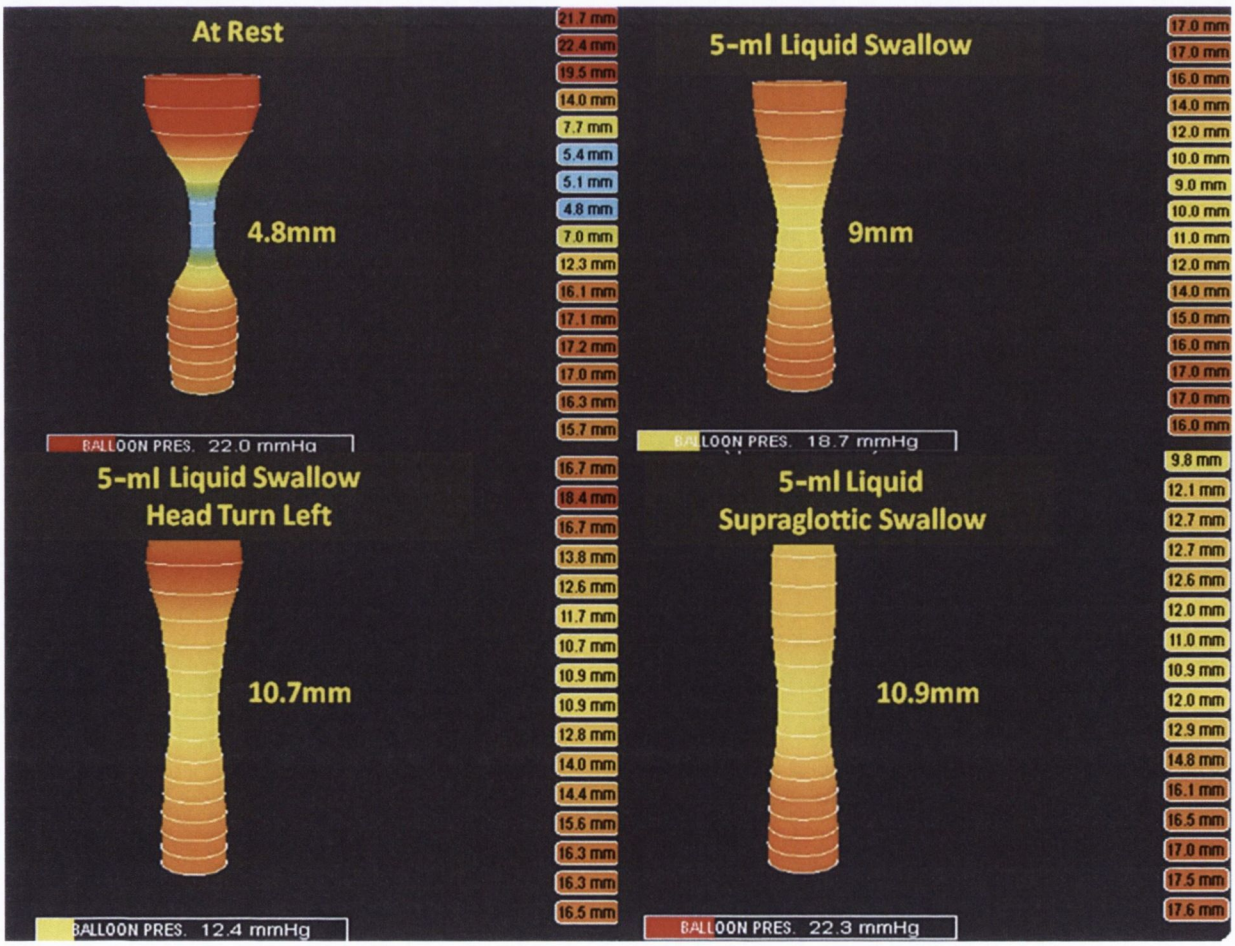

Fig. 5 Geometric profiles of upper esophageal sphincter on EndoFLIP® screen across voluntary maneuvers in a healthy subject.

Prolonged UES opening time in two cases[3,4] may represent a struggling behavior in initiating a pharyngeal swallow. Table 2 summarizes UES diameter and intraballoon pressure changes during various swallows events. The effects of swallow maneuvers on EndoFLIP geometric profile of the UES in an individual participant are detailed in Figure 5.

DISCUSSION

This preliminary study tested the use of FLIP to evaluate UES dynamics in a pilot group of healthy subjects. The FLIP balloon was positioned and distended in the UES without fluoroscopic guidance, and studies were completed without incident or adverse event. While all subjects tolerated FLIP placement in the UES region, one of 11 subjects could not tolerate the inflated probe in the UES for prolonged periods to complete the study protocol. Further studies will need to be completed to establish tolerance levels.

During distensibility testing, ramp distensions were conducted to a lower maximum volume (20 mL) than EGJ studies to ensure that the airway was not impinged. Nevertheless, the hourglass shape of the UES could be observed across subjects (Fig. 3), and mean intraballoon pressure and UES CSA increased (Table 1).

Maximum UES diameters during dry and liquid swallowing as measured by FLIP are similar to videofluoroscopy measures[2] (Fig. 1). Albeit with varying balloon volumes (12 or 15 mL), FLIP also established mean effects of voluntary maneuvers on extent of UES opening (Table 2). Effectiveness of strategies could be determined within evaluations because of real-time geometric profile of the UES on the EndoFLIP screen.

Of note, the minimal detectable diameter of the EndoFLIP probe is 4.8 mm (or 18.1 mm^2) because of its physical size. Therefore, if the probe measures 4.8 mm, the actual value may be smaller. This is a source of error that may make the deviation of data, for these small measurements seem less than they actually are. Additionally, FLIP does not provide real information on the actual luminal shape in the UES region. However, from this and studies of other regions (i.e. EGJ), we know that it is representative of function, particularly as it relates to the distension required to open the sphincter and representing that opening as a measure of multiple radial cross-sectional areas.

In future studies, confounding effects of factors (e.g. anxiety) on UES measurement should be minimized (e.g. habituation period). Optimal balloon positioning and volume during testing need to be established. Reproducibility of FLIP data and most appropriate data analysis require investigation.

Preliminary findings suggest that FLIP can provide novel and clinically useful quantitative measures regarding UES dynamics. Objective information regarding UES opening is clinically valuable and is lacking because of subjectivity and poor interreliability of videofluoroscopic analysis.[3] Research is currently underway to further explore the role of FLIP in UES evaluation.

Acknowledgments

J.R., B.M., and M.W. designed study. J.R., N.R., and B.M. collected data. J.R. analyzed data and wrote paper. M.W., N.R., and B.M. reviewed paper. This work was funded by the Health Research Board, Ireland (Grant HPF/2009/39). This work was presented orally, in part, at the Dysphagia Research Society conference, Texas, 2011.

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New measures of upper esophageal sphincter distensibility and opening patterns during swallowing in healthy subjects using EndoFLIP®

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Abstract

Background *This paper aims to measure upper esophageal sphincter (UES) distensibility and extent and duration of UES opening during swallowing in healthy subjects using EndoFLIP®.* ***Methods*** *Fourteen healthy subjects (20–50 years) were recruited. An EndoFLIP® probe was passed trans-orally and the probe balloon was positioned across the UES. Two 20-mL ramp distensions were completed and UES cross-sectional area (CSA) and intra-balloon pressure (IBP) were evaluated. At 12-mL balloon volume, subjects completed dry, 5- and 10-mL liquid swallows and extent (mm) and duration (s) of UES opening and minimum IBP (mmHg) were analyzed across swallows.* ***Key Results*** *Thirteen subjects completed the study protocol. A significant change in UES CSA ($P < .001$) and IBP ($P < .000$) was observed during 20-mL distension. UES CSA increased up to 10-mL distension ($P < .001$), from which point IBP raised significantly ($P = 0.004$). There were significant changes in UES diameter (mm) ($P < .000$) and minimum IBP (mmHg) ($P < .000$) during swallowing events. Resting UES diameter (4.9 mm; IQR 0.02) and minimum IBP (18.8 mmHg; IQR 2.64) changed significantly during dry (9.6 mm; IQR 1.3: $P < .001$) (3.6 mmHg; IQR 4.1: $P = 0.002$); 5 mL (8.61 mm; IQR 2.7: $P < .001$) (4.8 mmHg; IQR 5.7: $P < .001$) and 10-mL swallows (8.3 mm; IQR 1.6: $P < 0.001$) (3 mmHg; 4.6: $P < .001$). Median duration of UES opening was 0.5 s across dry and liquid swallows ($P = 0.91$). Color contour plots of EndoFLIP® data capture novel information regarding pharyngo-esophageal events during swallowing.* ***Conclusions & Inferences*** *Authors obtained three different types of quantitative data (CSA, IBP, and timing) regarding UES distensibility and UES opening patterns during swallowing in healthy adults using only one device (EndoFLIP®). This new measure of swallowing offers fresh information regarding UES dynamics which may ultimately improve patient care.*

Keywords *deglutition, dysphagia, evaluation, FLIP, swallowing, upper esophageal sphincter.*

INTRODUCTION

The upper esophageal sphincter (UES) is a muscular constriction separating the pharynx and the esophagus. It consists of inferior pharyngeal constrictor (IPC) muscles, the cricopharyngeus (CP), and the cervical esophagus (CE), which create a 2–4 cm high pressure zone.[1] UES high resting tone prevents diversion of air into the esophagus during inspiration and protects the airway from any retrograde passage of material refluxed from the esophagus or stomach. During swallowing, the UES needs to open adequately to ensure material passes safely and efficiently from the pharynx into the esophagus. This begins with CP relaxation and is followed closely by anterior and

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superior hyo-laryngeal excursion to stretch open the UES. Pressure from the oncoming bolus further distends the UES lumen.[2]

Impaired UES opening is a feature of crico-pharyngeal dysphagia which frequently leads to tracheal aspiration and pharyngeal retention post swallow. It is commonly associated with neurological conditions (e.g., brainstem stroke, amyotrophic lateral sclerosis), myopathy (e.g., fibrosis), and structural abnormalities (e.g., Zenkers diverticulum, CP bar).[3–7] Treatment depends on the underlying cause and can include compensatory postures (e.g., head turn), rehabilitation (e.g., Shaker head lifting exercises), pharmaceutical and surgical intervention (e.g., botulinum toxin or CP myotomy).[8–11] Objective and reliable UES evaluation is critical to determine the presence and nature of UES dysfunction and to ensure that the safest and most effective dysphagia intervention is provided. Currently, videofluoroscopy and pharyngeal manometry are the most commonly employed UES evaluations. However, several limitations to these evaluations have been identified including unacceptable interrater reliability of UES opening measures and varying resting UES pressure ranges between 35 and 200 mmHg across studies.[12–16]

The functional lumen imaging probe (FLIP) is a novel distensibility tool based on the principles of impedance planimetry.[17] A balloon at the distal end of a FLIP probe is positioned in an anatomical lumen and is distended by filling it with a conductive solution. Functional lumen imaging probe provides multiple CSA measures of the lumen and uses these to recreate a functional dynamic image of sphincter geometry. These CSA measures, alongside a measure of intra-balloon pressure, facilitate measurement of sphincter distensibility.[18] Functional lumen imaging probe was originally designed to evaluate esopho–gastric junction (EGJ) compliance.[19] It has since been employed to evaluate other anatomical sites including the sphincter of Oddi, the upper esophagus, and laparoscopic lumens.[20–23]

Until recently, the role of FLIP in UES evaluation had not been explored. Two studies have demonstrated safe insertion and distension of the FLIP balloon in the UES of healthy adults and patients with dysphagia both with and without videofluoroscopic guidance.[24,25] The derivation of preliminary UES distensibility data and novel quantitative UES diameter and intra-balloon pressure measures by FLIP without fluoroscopy has also been reported.[25] Based on these initial studies, authors hypothesize that FLIP may provide new information on UES opening characteristics during distension and may provide objective measures of UES opening during swallowing. The aims of this study were (i) to measure UES distensibility using FLIP in a group of healthy adults, and (ii) to quantify UES opening during dry and liquid swallowing events in this healthy group using FLIP.

MATERIALS AND METHODS

Subjects

Subjects were recruited from a pool of healthy volunteers. Inclusion criteria were (i) no history of oro-pharyngeal or esophageal dysphagia, (ii) no history of gastrointestinal, neurological, or respiratory disease, and (iii) no history of head and neck cancer or ear, nose and throat conditions. Fourteen subjects (six males, eight females) with a mean age of 30 years (age range 20–50 years; SD = 11.02) met inclusion criteria. Written consent was obtained from subjects. Ethical approval was obtained from the Research Ethics Committee, University Hospitals Leuven, Belgium.

EndoFLIP® system

A commercially developed FLIP (EndoFLIP® system; Crospon Ltd., Galway, Ireland) was used. In brief, a polyurethane balloon with a maximum volume of 60 mL is mounted on the distal 14 cm of a probe (EF-325) (length 240 cm, diameter 25 mm) attached to the EndoFLIP® unit. This balloon assumes a 10 cm long cylindrical shape with maximum diameter of 2.5 cm when fully filled. The maximum balloon diameter is critical to prevent airway compromise during balloon distension. Along a 7.5 cm segment within the balloon, 17 ring electrodes are spaced 5 mm apart to obtain 16 CSA measurements using an impedance planimetry technique. This allows diameter and pressure changes above (i.e., pharynx) and below (i.e., upper esophagus) the UES to be captured and for UES opening to be observed despite its upward shift during swallowing. Excitation electrodes situated at either end of the 17 ring electrodes emit a constant low electrical current within the balloon. The probe also contains a solid-state pressure transducer to measure intra-balloon pressure. EndoFLIP is CE marked under the European device directive and has been approved for inflation in the esophagus. Fill volumes were limited to a maximum of 20 mL in this study in a balloon that can hold 60 mL. The EndoFLIP® system was also pressure limited. The upper limit was set at 80 mmHg based on pilot studies. If this set pressure limit is reached, the system will stop the inflation and the alarm will sound.

Protocol

The EndoFLIP® system was positioned beside the subject who was seated upright on a chair within the clinic room (Neurogastroenterology & Motility Clinic, University Hospital Leuven). The equipment was powered on and both the syringe and a precalibrated probe were connected to the EndoFLIP® unit. An automated purge sequence initiated by the EndoFLIP® removed air from the balloon and calibrated the pressure measurement inside. Topical anesthesia (Lignocaine spray) was administered to the posterior pharyngeal wall and subjects were instructed to perform a dry swallow. The tip of the EndoFLIP® probe was lubricated and inserted orally by a member of the research team until the deflated balloon at the distal end of EndoFLIP® was

judged to have passed into the proximal esophagus (30 cm marking on EndoFLIP® catheter). The subject was transferred to a bed and seated in a 90° angle upright position. The EndoFLIP® catheter was held outside of the subjects' teeth by a researcher to minimize displacement during the evaluation.

When the subject became accustomed to the probe, the probe balloon within the esophagus was distended with 10 mL saline solution from the syringe using a touch screen function on the EndoFLIP® monitor. The inflated balloon was then slowly retracted until the hourglass shape of the UES could be visualized on the EndoFLIP® display (17–20 cm marking on EndoFLIP® catheter; Fig. 1). This confirmed the balloon position in the UES. While holding the catheter in place, the balloon was deflated.

After a brief habituation period (1–2 min), two ramp distensions to 20 mL were completed (rate 60 mL min^{-1}). Subjects were requested not to swallow during distensions and the EndoFLIP® screen was monitored to ensure the balloon remained in position. Two distensions were completed to allow for an accommodation effect. The balloon was then reinflated with a 12 mL volume of conductive solution. 12-mL balloon volume was selected as it was well tolerated during pilot studies and yet sufficient a volume to observe an hourglass shape on the EndoFLIP® screen when positioned in the UES. Once a baseline measure of minimum UES diameter (mm) and intra-balloon pressure (mmHg) was recorded, subjects were asked to complete the following:

(a) two dry swallows
(b) two 5-mL liquid swallow delivered orally via a syringe
(c) two 10-mL liquid swallow delivered orally via a syringe.

A minimum 10-s time period between the performances of each swallow was enforced to easily identify events during data analysis. The time (in seconds) displayed on the EndoFLIP® device at the execution of each swallow was recorded. When the protocol was completed, 12 mL was deflated from the balloon and the probe was removed.

Data analysis

UES distensibility EndoFLIP® provides 16 measures of CSA (mm^2) and a measure of intra-balloon pressure (mmHg) at a rate of 10 Hz during distensions. Data from the second 20-mL ramp distension were transferred from EndoFLIP® into an Excel document on a personal computer. Median CSA (mm^2) and intra-balloon pressure (mmHg) measures and interquartile ranges (IQRs) were determined at 1, 5, 10, 15, and 20-mL balloon volumes across subjects.

Swallow events EndoFLIP® measures of diameter, intra-balloon pressure, and time were transferred into an Excel document. To determine change in UES opening during swallowing, three EndoFLIP® measures were selected for examination at rest and during second dry, 5- and 10-mL liquid swallow events. There were (i) extent of UES opening (mm), (ii) duration of UES opening (ms), and (iii) minimum intra-balloon pressure (mmHg). The derivation of each variable is described below.

1 Extent of UES Opening (mm): EndoFLIP® provides 16 estimated diameter (mm) measurements (based on CSA) at a rate of 10 s^{-1} throughout the examination. The minimum of the 16 diameter measures at each time point was considered to be the narrow UES region (Fig. 1B). This minimum UES diameter measure was evaluated during swallow events to ascertain the extent of UES opening during swallowing. Of note, the minimal detectable diameter of the EndoFLIP® probe is 4.8 mm (or 18.1 mm^2) because of its physical size.
2 Duration of UES opening (ms): Sixteen diameter measures were provided by EndoFLIP® at a rate of 10 s^{-1}. Duration of UES opening was defined as the time from which the narrowest diameter in the UES region sharply rises from its baseline during swallowing until its return to baseline diameter (Fig. 1B).
3 Minimum intra-balloon pressure (mmHg): FLIP provided 10 measures of intra-balloon pressure (mmHg) per second (Fig. 1B). To examine change in intra-balloon pressure observed during swallow events, the minimum pressure measurement during swallowing was examined across swallows.

Statistical analysis

Data were entered into SPSS statistical software package (version 19) (IBM CORP, Armonk, NY, USA). Based on Shapiro–Wilk tests, all data were not normally distributed. Data were therefore expressed as medians (IQR) and non-parametric tests were employed. Kruskal–Wallis tests were used to determine a change in UES CSA and intra-balloon pressure across balloon volumes (1,

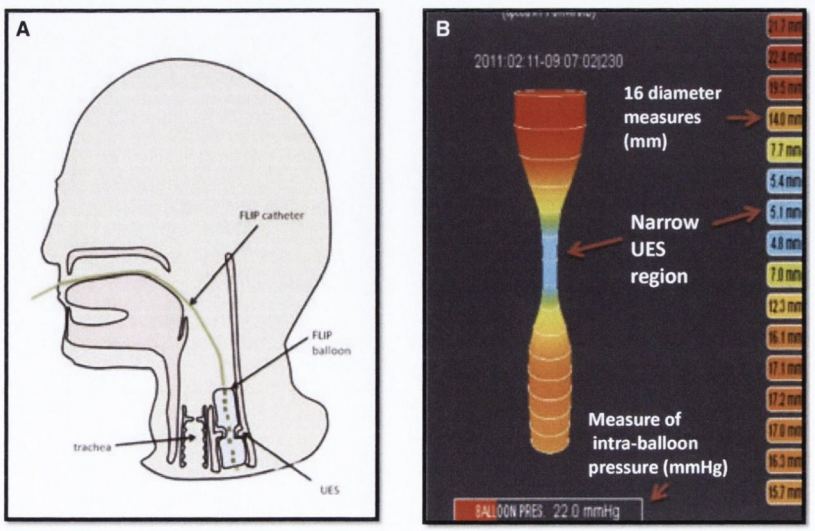

Figure 1 Positioning of EndoFLIP® Balloon in UES of Healthy Subjects. This is an approximate representation of the proportions of anatomical landmarks.

5, 10, 15, and 20 mL) during distensibility testing and to establish differences in UES diameter, minimum intra-balloon pressure and duration of UES opening at baseline and across dry, 5- and 10-mL liquid swallow events. Significance was set at $P < .05$. Where significance was found, multiple comparisons were made using the Wilcoxin rank sum test. Bonferroni correction was made and post hoc tests were significant at an adjusted alpha level of 0.0127 for distensibility testing and 0.008 for swallow events.

RESULTS

UES distensibility

The EndoFLIP® probe was safely inserted and the narrowing of the UES was identified on the EndoFLIP® screen across all 14 subjects. Thirteen of 14 subjects completed 20-mL ramp distensions. One subject (subject 11) was unable to tolerate more than 16 mL in the inflated balloon in the UES for prolonged periods. The data from this subject were therefore omitted from distensibility data analysis. The second of two 20-mL ramp distensions was included in data analysis to allow for an accommodation effect. One subject (subject 13) did not reach a maximum of 20-mL balloon volume on their second distension (18 mL) and hence their first distension (20 mL) was selected for data analysis.

Across all subjects, the hourglass shape of the UES could be visualized on the EndoFLIP® screen during the ramp distension. A representative geometric profile of the UES on the EndoFLIP® screen which was observed across all subjects at 20-mL balloon volume is shown in Fig. 1. The minimum UES CSA increased significantly during the 20-mL ramp distension as the balloon volume increased [$H(2) = 18.32$, 4 d.f., $P < .001$; Fig. 3]. A nearly significant increase in median UES CSA was found between 1 m and 5-mL balloon volumes (median CSA 18.7 and 22.5 mm^2, respectively; $P = 0.028$) and there was a significant increase in UES CSA between 5- and 10-mL balloon volumes (median CSA 22.5 and 23.8 mm^2, respectively; $P < .001$). The UES then resisted any further increase in CSA during the distension, as no difference in median CSA was observed between 10 and 154 mL ($P = 0.382$) or between 15 and 20 mL ($P = 0.382$) (Fig. 2).

Intra-balloon pressure also increased significantly during the 20-mL ramp distension [$H(2) = 27.36$, 4 d.f., $P < .000$; Fig. 3]. No significant difference in median intra-balloon pressure was found between 1 and 5 mL ($P = 0.463$) or between 5 and 10 mL ($P < .861$). However, once balloon inflation caused the UES CSA to reach a plateau, a significant increase in intra-balloon pressure was detected between 10 and 15 mL (4 and 13.4 mmHg, respectively) ($P = 0.004$) and between 15 and 20 mL (13.4 and 36.9 mmHg, respectively; $P = 0.003$, Fig. 2).

Swallow events

Thirteen of 14 subjects completed the entire swallow events protocol with the distended EndoFLIP® balloon (12 mL) within the UES. One subject (subject 12) could not tolerate the distended balloon in the UES for the entire protocol and was omitted from swallow maneuvers data analysis. Data at rest and from 39 swallows (the second dry, 5- and 10-mL liquid swallows) within the subject group were analyzed to obtain group measures of UES diameter, minimum intra-balloon pressure and duration of UES opening across swallow events.

There was a statistically significant change in UES diameter across swallow events ($P < .000$). During dry swallowing, UES diameter increased from a baseline diameter measure of 4.9–9.6 mm (IQR 1.3; $N = 13$, $P < .001$). Resting median UES diameter increased from 4.9 to 8.61 mm (IQR 2.7) during five liquid swallows ($P < .001$). Diameter increased from 4.9 mm at baseline to 8.27 mm (IQR 1.6) during 10-mL liquid swallows ($P < .001$). A significant median difference was also observed in UES diameter between dry and 10-mL liquid swallows ($P < .005$). However, no significant difference in UES diameter was observed during dry and 5-mL swallows ($P = 0.64$) or between 5- and 10-mL liquid swallows ($P = 0.46$; Fig. 3).

No significant difference was evident in duration of UES opening across swallow events ($N = 13$, $P = 0.91$; Fig. 3). Median duration of UES opening remained at 0.5 s across subjects during dry swallowing (IQR 0.3), 5-mL liquid swallows (IQR 0.3), and 10-mL liquid swallowing (IQR 0.1; Fig. 3).

A statistically significant difference in minimum intra-balloon pressure was observed across swallow events ($P < .000$). Minimum intra-balloon pressure dropped from 18.8 mmHg at rest to 3.6 mmHg (IQR 4.1) during dry swallowing ($P = 0.002$). Minimum intra-balloon pressure dropped from 18.8 mmHg at baseline to 4.8 mmHg (IQR 5.5) during 5-mL swallows ($P < 0.001$; Fig. 3). Pressure dropped from 18.8 to 2.96 mmHg (IQR 4.6) during 10-mL liquid swallows ($P < 0.001$). There was no significant difference in minimum pressure between dry and 5-mL ($P = 0.6$) or 10-mL ($P = 0.86$) swallows or between 5- and 10-mL swallows ($P = 0.35$; Fig. 3).

Using OriginLab data analysis software (version 8.6), EndoFLIP® diameter, pressure, and time measurements are displayed in color contour plots at rest and during swallowing (Fig. 4).

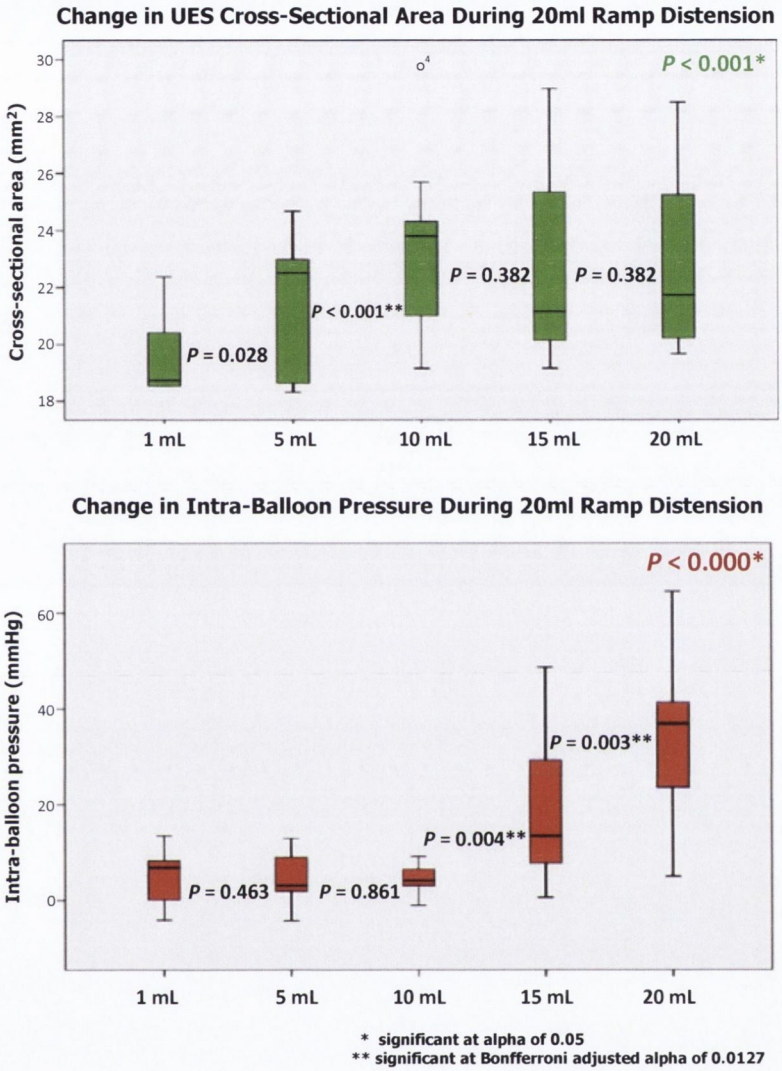

Figure 2 Median CSA & intra-balloon pressure changes during 20-mL ramp distension across subjects (N = 13).

DISCUSSION

In this study, distensibility and opening patterns of the UES were evaluated for the first time in a group of 14 adult healthy subjects using EndoFLIP®. EndoFLIP® was well tolerated within the UES in this subject group (13 of 14 subjects), with tolerance and comfort levels similar to fiberoptic endoscopic evaluation of swallowing (FEES).[26,27] The UES was identified across all subjects during the 20-mL ramp distension. Major findings included the significant increase in the CSA of the UES lumen during distensibility testing. Specifically, UES CSA distended up until 10-mL distension and then resisted further distension. This resistance was presumably due to the high resting UES tone within this healthy non-elderly subject group. From this point, intra-balloon pressure raised significantly.

This was the first study to analyze compliance of the UES lumen using EndoFLIP® in healthy adults. EndoFLIP® measurement of UES dynamics may contribute to our understanding of UES function and dysfunction and may, in the longer term, enhance diagnosis and hence the rehabilitative or surgical treatment of dysphagia. Further studies will determine if a distinction in UES distensibility is evident between non-elderly and elderly subjects or between healthy and clinical groups with known UES dysfunction (e.g., CP hypertonicity, CP fibrosis). The effects of different bolus consistencies on UES opening during swallowing as measured by FLIP need to be evaluated. Beyond an initial study to demonstrate this technique, no other studies have used EndoFLIP® to evaluate UES distensibility to date. In a separate study, work has begun to compare FLIP measures of UES opening to data from

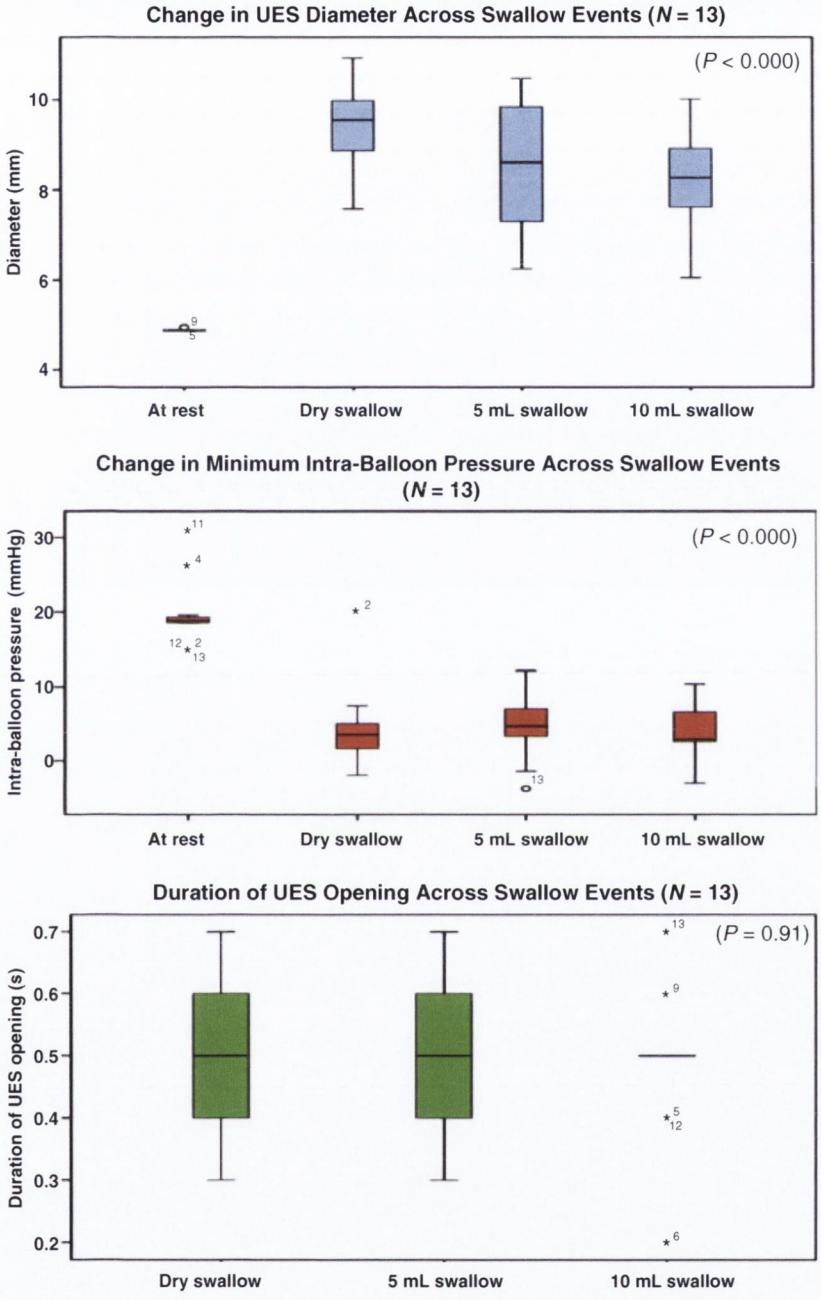

Figure 3 UES diameter, intra-balloon pressure, and duration of UES opening at rest and during Dry, 5- and 10-mL liquid swallows (N = 13).

other UES diagnostic tools within the same subject group.

This study also sought to examine extent and duration of UES opening during dry and liquid swallow events using EndoFLIP®. This information is currently difficult to quantify reliably in clinical dysphagia practice.[28] EndoFLIP® provided quantitative measures of the extent and duration of UES opening and intra-balloon pressure changes over time during dry and liquid swallowing events. Significant changes in UES diameter and minimum intra-balloon pressure during swallowing events were found. Extent of UES opening was quantitatively measured and ranged between 8.3 and 9.6 mm across dry, 5- and 10-mL liquid swallows in this study. Videofluoroscopy studies have found that extent of UES opening in healthy adults has ranged between 8 and 12 mm during swallowing[6,29–31] (Fig. 5). Duration of UES opening was 0.5 s across bolus volumes in this study. Measures of duration of UES opening also closely matched duration measures in previous videofluoroscopy research[6,29–31] (Fig. 5). Although measures of UES

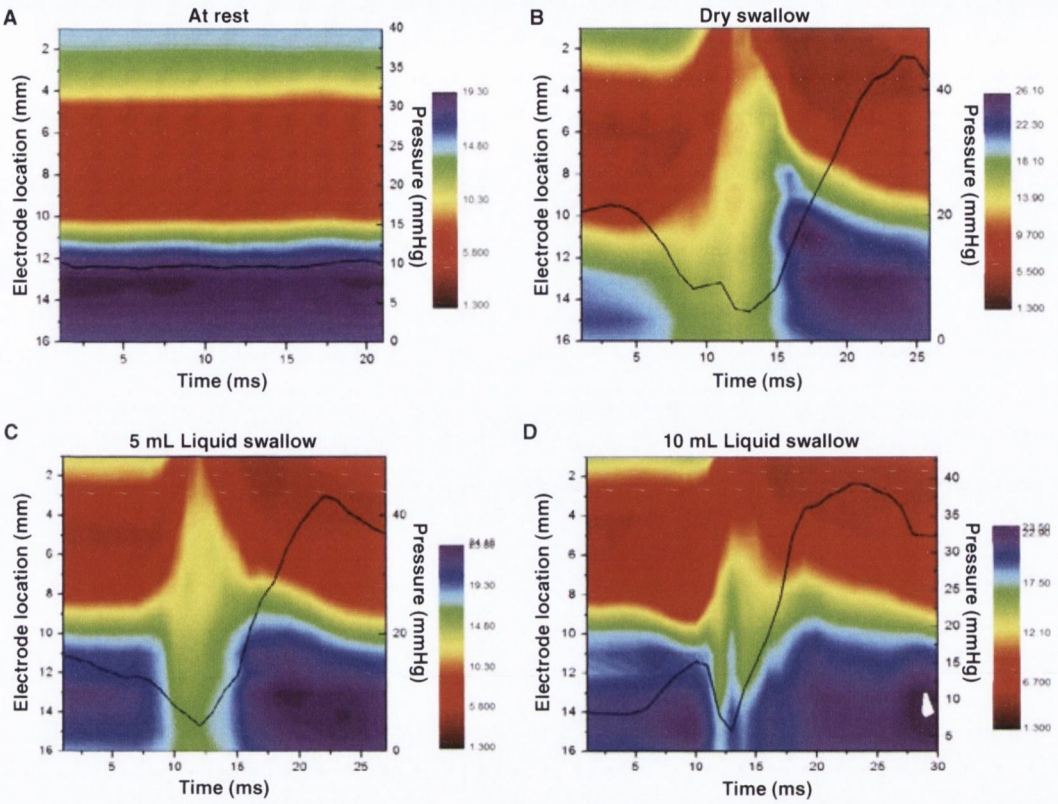

Figure 4 Color contour plots of EndoFLIP® diameter, intra-balloon pressure, and time measures during dry, 5- and 10-mL liquid swallows. Color contour plots depict diameter and intra-balloon pressure changes over time. Time is on the *x*-axis and 16 diameter measurements from 17 detection electrodes spaced 5 mm apart within the EndoFLIP® balloon are displayed on the *y*-axis. Each diameter measure is assigned a color (see legend). The narrowest diameter measures (in red) are at the level of the UES. The black line represents intra-balloon pressure over time. (A) The narrow band of UES (median diameter 4.9; IQR 0.02) is observed at rest over time. At rest, the median length of the UES was 3 cm (IQR 1.7; mean 3.3 cm) across subjects. As the EndoFLIP® balloon is 10 cm in length, an increased diameter is visible above and below the UES region, representing the pharynx and upper esophagus, respectively. Median resting intra-balloon pressure is 18.8 mmHg (IQR 2.7) over time across subjects. (A) Resting UES diameter is 4.9 mm and the resting length of the UES is 4 cm. As (4B–D) the swallow is elicited, (C) a drop in intra-balloon pressure from its baseline shortly precedes a 2 cm upward shift of the UES, presumably caused by hyo-laryngeal excursion due to suprahyoid muscle contraction. Due to the 5 mm spacing between electrodes, the extent of this upward shift during swallowing can be quantified on the color contour plot. The UES lumen then opens to 9 mm during swallowing. At the point of UES opening, intra-balloon pressure reaches its minimum point. A narrowing within the upper esophagus is evident at the point of UES opening, perhaps due to peristalsis as the bolus enters the esophagus. The UES then closes and intra-balloon pressure increases markedly. The UES returns to its resting position and intra-balloon pressure gradually decreases.

opening were similar to other techniques, EndoFLIP® data are not labor intensive to acquire and geometric changes in the UES during swallowing can be observed in real time on the portable EndoFLIP® device as a biofeedback tool without any need for fluoroscopy.

In this study, extent of UES opening was largest for dry swallowing compared with 5- and 10-mL liquid swallows. Intra-balloon pressure during swallowing did not decrease with increase bolus volume and duration of UES opening remained the same across dry, 5- and 10-mL liquid swallows. This lack of volume effect has also been reported in videofluoroscopy and pharyngeal manometry-impedance studies.[32,33] However, as swallow events were not randomized within the study protocol, a lack of volume effect between dry and 10-mL liquid swallows may have been due to an accommodation or fatigue effect.

When diameter, pressure, and time data provided by EndoFLIP® are depicted in color contour plots, professionals are provided with an innovative graphic display of the extent and duration of UES opening on a time axis during swallowing. As detection electrodes within the probe balloon are spaced only 5 mm apart, EndoFLIP® can provide a rich profile of UES dynamics during swallowing and can represent the relationship between UES opening and intra-balloon pressure. Patterns regarding the sequence and duration of diameter and pressure changes were apparent across swallows in this healthy subject group and may, based on future studies, define whether bolus transport through the UES is normal or impaired. Future validation of

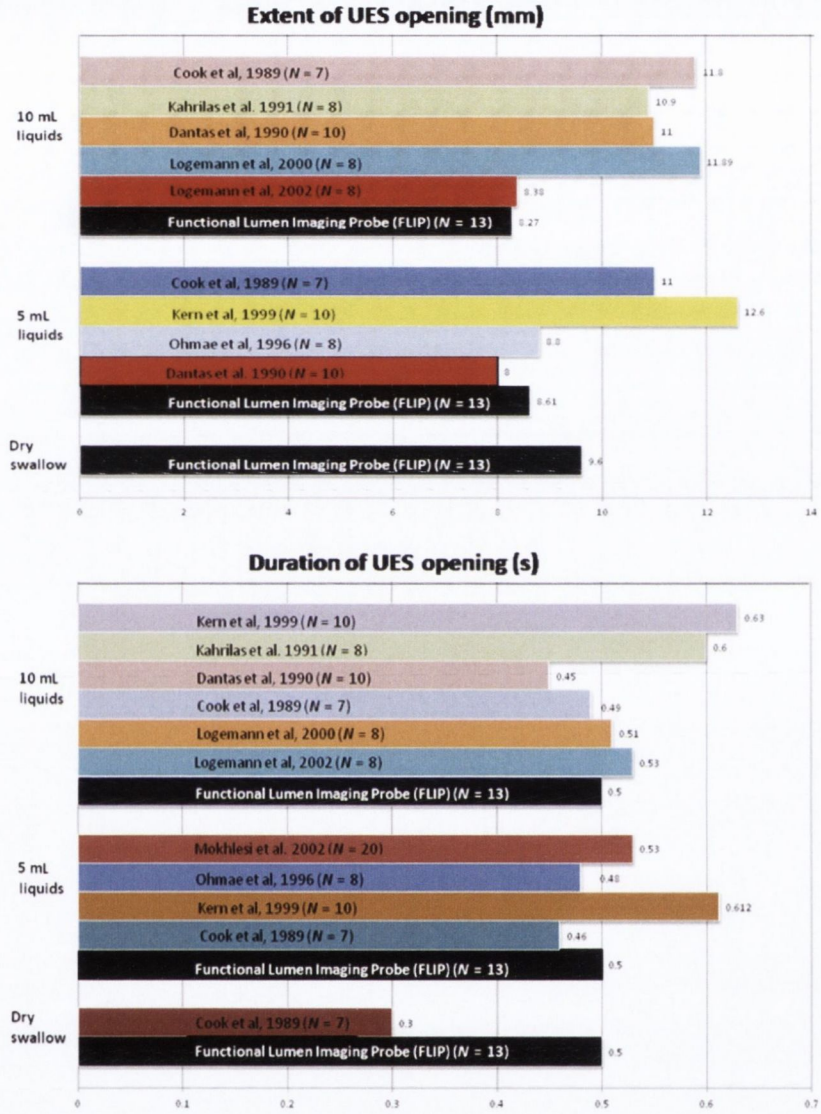

Figure 5 Comparison of FLIP measures of extent and duration of UES opening during swallowing to previous videofluoroscopy research.

EndoFLIP® data with measures from other physiological examinations may assist in determining if the various phases of UES opening (e.g., CP relaxation) are captured by EndoFLIP®. Data in this study suggest that other pharyngo-esophageal events such as the upward shift of the UES during swallowing secondary to hyo-laryngeal excursion have the potential to be quantified based on these plots. This information may, in clinical practice, determine efficacy of or candidacy for rehabilitation (e.g., Shaker exercises) or surgical interventions such as botulinum toxin injections or CP myotomy.[9–11]

Pharyngo-esophageal swallowing events observed in EndoFLIP® color contour plots do present similarly to spatiotemporal pressure events on high-resolution manometry (HRM).[34] The important distinction, however, is that EndoFLIP® measures changes in the narrowing of a lumen during swallowing, whereas HRM measures of UES opening are based on pressure changes during swallowing. It is hoped that the development of new physiological gastrointestinal tests such as multi-channel intra-luminal impedance, high-resolution manometry, and EndoFLIP® may lead to better diagnostic precision and hence tailor clinical dysphagia intervention. The use of a balloon to study UES dynamics avoids the issue of pressure sensor displacement from the UES during swallowing as seen in traditional manometry.

Potential limitations to this study include the fact that only 10 diameter recordings are provided per

second by EndoFLIP®. This may have limited measures of duration of UES opening as peak values may have been missed between measurements. However, a good range of values was apparent within the subject group. These values of UES opening duration were also in keeping with previous videofluoroscopy research.[6,29,30] Otherwise, the minimum diameter measure provided by EndoFLIP® is 4.8 mm, which may be narrowing some UES diameter data ranges. Perhaps one of the most important issues to consider based on this study is the optimum EndoFLIP® balloon dimensions and volumes for UES evaluation. While the study protocol was adapted from EGJ studies for UES evaluation, the probe used in these studies is a standard version for use in other regions of the esophagus. These studies suggest that EndoFLIP® balloon length and positioning need to be carefully considered during future UES testing. Care had to be taken to ensure too much of the balloon was not positioned in the pharynx during testing. Otherwise, tolerance of the balloon decreased as subjects were very sensitive to the inflated balloon in the pharynx. Although a shorter probe balloon may address this issue to some extent, too short a balloon might prevent the UES opening from being captured due to its upward shift during swallowing. The effect of this can be seen most clearly on the color contour plots where the top end of the UES can disappear during swallowing as the UES opens. Refinement of balloon dimensions and positioning during the study protocol is of prime importance to ensure that critical information is not lost during data collection. Tolerance of the probe will continue to be monitored in future research with larger subject groups. FLIP also does not provide real information on the actual luminal shape in the UES region. However, from this and studies of other regions (i.e., EGJ), we know it is representative of function, particularly as it relates to the distension required to open the sphincter and representing that opening as a measure of multiple radial cross-sectional areas.

Future research should examine UES distensibility and opening patterns in elderly healthy adults and clinical groups with known UES dysfunction (e.g., CP hypertonicity) to determine the effect of aging and disease on UES compliance. It will be of interest to determine if those with electromyography (EMG)-confirmed disordered CP relaxation present differently during UES distensibility testing to those with pharyngeal phase involvement (i.e., poor hyo-laryngeal excursion or weak intra-bolus pressure). Validation of EndoFLIP® against a gold standard assessment will determine the sensitivity of EndoFLIP® in diagnosing aspects of dysphagia. The development of any additional outcomes measures based on diameter, intra-balloon pressure, and time data obtained from EndoFLIP® needs to be explored.

CONCLUSIONS

This study presented a new technique to measure UES distensibility and to quantify the extent and duration of UES opening during swallowing events. EndoFLIP® was well tolerated by subjects and it provided valuable objective information regarding UES compliance without need for fluoroscopy. It also provided novel quantitative measures of UES opening during swallowing events which are currently lacking in clinical practice. Results on the diameter and timing of UES opening during swallow match with current knowledge on UES physiology. However, FLIP data obtainable at the bedside without need for contrast material or radiation. Color contour plots representing EndoFLIP® diameter and pressure data on a time axis provide a novel objective approach to the analysis of UES dynamics during swallowing. EndoFLIP® may provide a role in evaluating UES opening during swallowing in patients with dysphagia before and after rehabilitation or surgery. Further research is currently underway to validate EndoFLIP® as a diagnostic tool in UES evaluation.

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DISCLOSURES

BM previously worked as a consultant for Crospon Ltd and is currently a minor shareholder in Crospon Ltd.

AUTHOR CONTRIBUTION

JR, MW, NR, & BM designed study; JR, MW, NR, JT, & BM collected data; JR analyzed data & wrote manuscript; MW, NR, & BM reviewed article.

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ABSTRACT

Thesis Title: Adaptation of the Functional Lumen Imaging Probe for Non-Radiological Evaluation of the Upper Oesophageal Sphincter.

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In this research, the Functional Lumen Imaging Probe (FLIP), a novel non-radiological measurement tool, was modified to evaluate upper oesophageal sphincter (UOS) distensibility and opening patterns during swallowing. Initially, accuracy of EndoFLIP® (a commercial FLIP device) diameter measurements was established during bench-top tests. To determine safety levels, the EndoFLIP® probe was inserted trans-nasally and positioned and distended in the UOS region of two individuals with oro-pharyngeal dysphagia under videofluoroscopy. Next, the EndoFLIP® probe was inserted trans-orally in five healthy adults without videofluoroscopic guidance. Based on these studies, a UOS evaluation protocol was developed and outcomes were defined.

In normative data studies, UOS distensibility was evaluated in fourteen non-elderly (20-50 years) healthy subjects using EndoFLIP®. Thirteen subjects tolerated the evaluation. There was a statistically significant increase in UOS cross-sectional area up to 10mls during a 20ml ramp distension from which point it plateaued. There was a statistically significant increase in intra-balloon pressure from 10ml to 20ml balloon volume during distension test. These findings indicated adequate UOS tone in this healthy non-elderly group. Next, quantitative measures of UOS opening during swallowing were obtained across bolus volumes in the same subject group (N=14) using EndoFLIP®. Measures were comparable to previously published videofluoroscopy findings. Differences in UOS distensibility and UOS opening measures during swallowing were identified across genders. EndoFLIP® temporal, diameter and pressure data was used to create colour contour plots of swallow events which provide a novel means to visualise UOS patterns during swallowing. The effects of commonly employed voluntary postures and manoeuvres on UOS opening were investigated using EndoFLIP® (N=11). Postures and manoeuvres significantly altered all EndoFLIP® measures of UOS opening. During swallowing, the Mendelsohn manoeuvre significantly increased duration of UOS opening and the supraglottic swallow significantly reduced minimum intra-balloon pressure.

To initiate the validation process, EndoFLIP® measures of UOS opening during swallowing were compared to automated impedance manometry (AIM) analysis parameters based on combined high-resolution manometry and multi-channel intra-luminal impedance studies (N=11). There was a statistically significant correlation between EndoFLIP® measures of extent and duration of UOS opening and numerous AIM analysis measures including pressure at nadir impedance and flow interval.

To establish the clinical utility of EndoFLIP®, the measurement tool was used to evaluate distensibility of the reconstructed pharyngo-oesophageal segment (POS) in ten patients with total laryngectomy. A 70% (7/10) tolerance rate of EndoFLIP® evaluation was observed. A statistically significant increase in POS CSA during distensibility testing suggested reduced POS tone post surgery. The POS opened less during swallowing across bolus volumes, although this was statistically insignificant. Duration of POS opening during swallowing was significantly longer across bolus volumes than in healthy controls. Finally, based on findings from an international 25-item online survey, the researcher found that just 17.9% (40/224) of dysphagia-trained SLTs are satisfied with current methods to evaluate the UOS.

This work contributes original quantitative information pertaining to UOS distensibility and opening patterns during swallowing which are currently lacking in dysphagia practice. Improved diagnostic UOS evaluation is necessary to improve our understanding of UOS function and dysfunction and to develop evidence-based dysphagia treatments. Directions for future research are proposed in order to complete the validation of EndoFLIP® in UOS evaluation.