Flinders University

High-resolution manometry with impedance for the assessment of age-related swallowing impairment (dysphagia)

By

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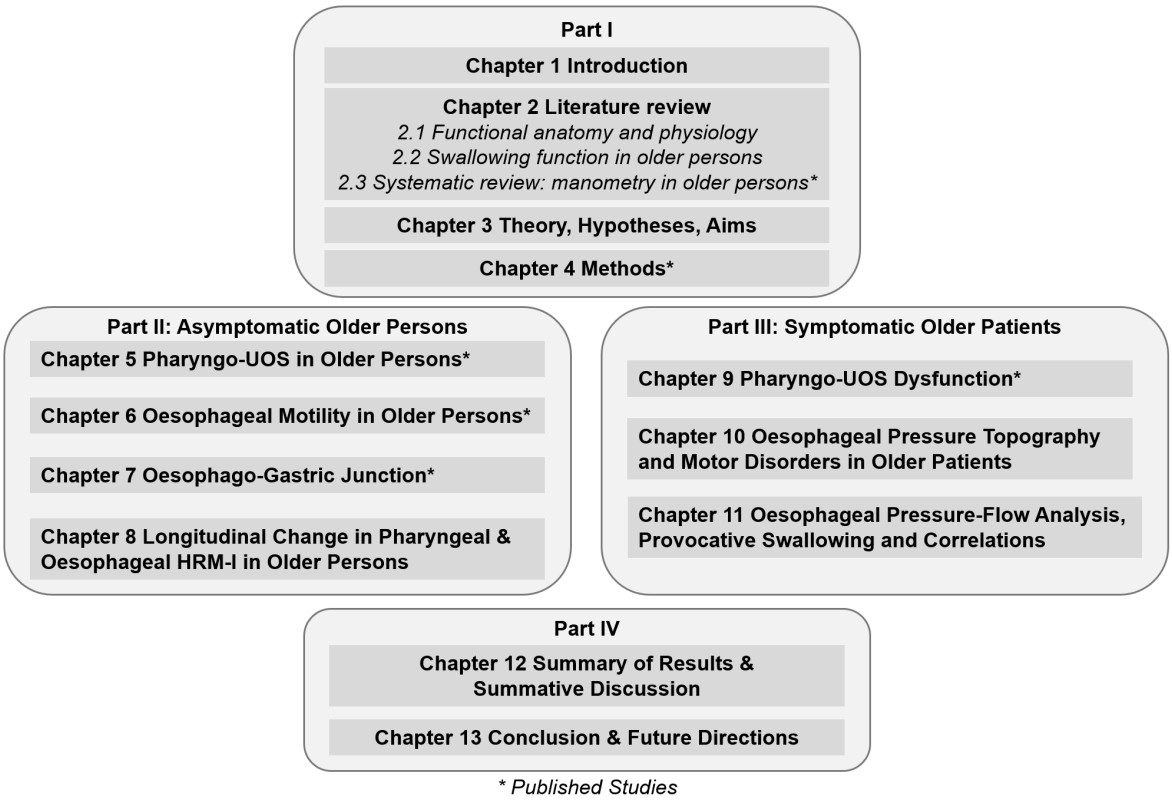

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Thesis Summary

Impaired swallowing (dysphagia) is common in ageing. The personal consequences for survival, health outcomes and quality of life are potentially devastating. The role of dysphagia in overall functional decline remains to be fully elucidated, with potentially a feed forward loop of dysphagia leading to sarcopenia, and in turn, further muscle weakness leading to increasing swallowing dysfunction.

This research program analysed high-resolution manometry with impedance (HRM-I) recordings from pharyngeal and oesophageal regions using novel pressure-flow analysis methods. The studies were focused on assessing how swallowing function changes in people and patients who are over 80 years of age, an age group for whom data of this kind are lacking.

The over 80s were compared to younger people and patients and, additionally, repeat measurements were collected over time to determine individual longitudinal changes.

Global pharyngeal function deteriorated with age. This deterioration was contributed to by upper oesophageal sphincter (UOS) dysfunction, evidenced by reduced UOS relaxation and opening. UOS dysfunction appeared to cause a downstream resistance to bolus flow that required a compensatory increase upstream pharyngeal propulsive force. In the over 80s, these forces were reduced, suggesting decompensation.

The apparently age-related changes on pharyngeal function were also linked to oesophageal dysmotility leading to failure of oesophageal bolus clearance in the over 80s and further exacerbated in patients reporting oesophageal symptoms.

This research program adds a significant evidence base for understanding of age-related swallowing dysfunctions.

Thesis + bibliography word count = 77957 words

Thesis Declaration

I certify that this thesis: 1. does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university 2. and the research within will not be submitted for any other future degree or diploma without the permission of Flinders University; and 3. to the best of my knowledge and belief, does not contain any material previously published or written by another person except where due reference is made in the text.

Charles Cock

Signed this day 15 March 2023, Adelaide, Australia

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CC

Part I

Chapter 1 Introduction

> Healthy ageing is "*the process of developing and maintaining the functional ability that enables wellbeing in older age", with functional ability defined as "having capabilities that enable all people to be and do what they have reason to value*" (WHO 2016).

The subject of this research program is to evaluate ageing-related changes in the functional abilities associated with swallowing. The ability to swallow, and therefore eat and drink, normally, is a critical aspect of wellbeing across the lifespan, providing the sustenance needed to survive and impacting on quality of life. Conscious or subconscious decline in swallowing function impairs both quality and quantity of life and swallowing disorders represent an underrecognized and underappreciated consequence of ageing (Cook 2009, Rommel & Hamdy 2016, Smithard 2016, Leslie & Smithard 2021).

Dysphagia, the difficulty, or discomfort in swallowing, is the conscious manifestation of disordered swallowing and is considered a disease state (Clavé & Shaker 2015, Rommel & Hamdy 2016). In contrast, a subtle decline in swallowing function, often manifest as the inability to swallow certain foods, and is often considered a normal part of ageing. This subtle decline in normal function commonly results in sub-conscious adaptation of eating or drinking behaviors to ensure safe and effective swallowing (Smithard 2016). In some older persons, this may even lead to normalizing manifest overt impairments by both the individuals themselves and their treating clinicians.

Due to its far reaching and multifaceted consequences, dysphagia in ageing, although perhaps underappreciated compared to other geriatric syndromes, has more recently been described as a *geriatric giant* (Smithard 2016, Baijens et al. 2016). Dysphagia in older persons

is intricately linked to malnutrition, sarcopenia and frailty (Baijens et al. 2016). In fact, the presence or onset of dysphagia is the key component of this *deadly quartet* (dysphagia, malnutrition, sarcopenia and frailty), which interrelates with *all* other components (Tsang et al. 2020), where sarcopenia is defined as a disorder involving the loss of skeletal muscle mass and function that commonly occurs with advancing age (Cruz-Jentoft et al. 2019). The advent of dysphagia in older persons is potentially a trigger for further functional decline (Tsang et al. 2020, Smithard 2020), resulting in a cascading *domino effect*, which leads to the eventual demise of some older persons. Its importance thus cannot be overemphasized. This thesis, therefore, presents my research program of studying, in detail, the biomechanics of age-related swallowing function and dysfunction using high-resolution impedance manometry.

This research program first tackled the fundamental question of how to best measure the biomechanics of swallowing function in ageing. This was a challenging question as it was critical to determine *what is normal* before evaluating swallowing pathology, especially when the consequences of dysfunction are potentially devastating in terms of both quality and quantity of life.

This thesis, therefore, consists of four major parts:

> Part I: Developing methodologies for the analysis of high-resolution impedance manometry in the pharynx, oesophagus and its sphincters;
>
> Part II: Normal function of the pharynx, oesophagus, and its sphincters in older persons;
>
> Part III: Abnormal function of the pharynx, oesophagus, and its sphincters in symptomatic older patients; &
>
> Part IV: Conclusion, Future Directions and Applications.

High-resolution manometry (1-2 cm spacing of pressure sensors) with oesophageal pressure topography, a two-dimensional representation of a multi-dimensional process, has markedly

enhanced our understanding of oesophageal physiology and its biomechanics over the past 10-15 years (Fox et al. 2004, Pandolfino et al. 2006, Fox & Bredenoord 2008, Pandolfino et al. 2009, Bredenoord et al. 2012, Kahrilas et al. 2015, Yadlapati et al. 2021). However, without using impedance data, which measures one of the fundamental physiological functions of the oesophagus, namely bolus transport (Tutuian et al. 2003, Tutuian & Castell 2004, Pandolfino & Bulsiewicz 2008, Bredenoord and Smout 2009, Bulsiewicz et al. 2009), interpretation of oesophageal manometry data is limited. Through including impedance, we can not only non-radiologically assess bolus transport (Tutuian et al. 2003, Tutuian & Castell 2004, Pandolfino & Bulsiewicz 2008, Bredenoord & Smout 2009, Bulsiewicz et al. 2009) but also better understand the interrelationship between pressure and bolus flow using a novel methodology called *pressure-flow analysis* (Omari et al. 2011, Chen et al. 2013, Rommel et al. 2014, Omari et al. 2014, Singendonk et al. 2015, Omari et al. 2016, Singendonk et al. 2019). Therefore, high resolution manometry *with* impedance was the key assessment tool used to measure swallowing function in my research program.

Through the work presented in Parts I & II, we are now able to measure swallowing biomechanics with great precision and can relate age-related changes in biomechanics to the relevant physiological functional outcomes, such as pulmonary aspiration of swallowed contents (Omari et al. 2011) or successful oesophageal bolus transport (Omari et al. 2016). We are also able to explore interrelationships between patient symptoms (or a lack thereof) with sensory mechanisms, swallowing muscle motor function (including during inhibition or excitation). As such, we are now approaching being able to understand swallowing *function* in order to understand *dysfunction*. Such understanding will assist in considered design of swallowing interventions to improve quantity, but more importantly, quality of life.

Of note, at the outset of this research program, no consistent manometric method existed to measure pharyngeal and upper oesophageal sphincter function in ageing. Indeed, the only widely accepted manometric analysis approach was the Chicago Classification system

(Pandolfino et al. 2009, Bredenoord et al. 2012, Kahrilas et al. 2015, Yadlapati et al. 2021), which only addresses distal oesophageal motor function with no consideration for preceding swallowing events in the pharynx, and to a large extent the proximal oesophagus (Omari & Schar 2018). In my view and clinical experience, preceding swallowing events can fundamentally interact with and modify the biomechanical and physiological function of subsequent components of the swallow (Triadafilopoulos et al. 1992, Gullung et al. 2012). Therefore, a large proportion of time was spent gathering data for Parts I & II of this thesis to inform an eventual pharyngeal classification (Omari et al. 2020, Omari et al. 2022), the background to which is described in methodology Chapter 4 and clinical application of in Chapter 9.

In summary, this thesis describes *normal* (in healthy volunteers) and *abnormal* (in patients) swallowing function, measured using high-resolution manometry with impedance, and analysed using pressure topography and pressure-flow methods in two anatomical regions:

A The Pharynx and Upper Oesophageal Sphincter (Pharyngo-UOS) &

B The Oesophagus and Oesophagogastric Junction (Oesophagus-OGJ).

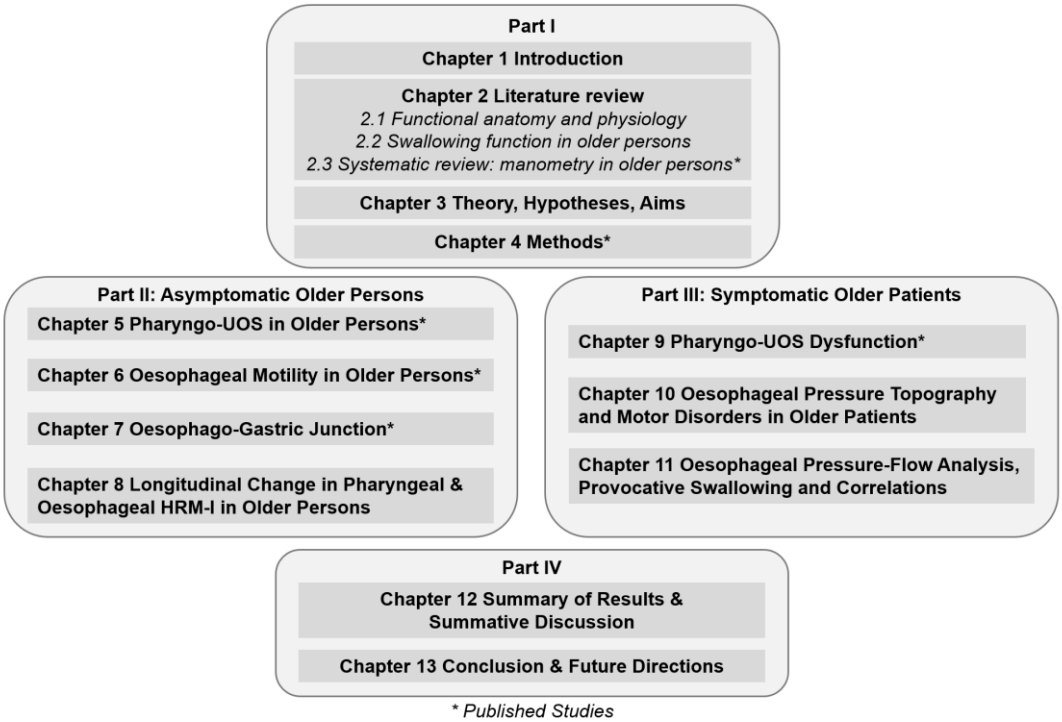

Figure 1.1 Outline of the Thesis

As outlined in Figure 1, after exploring a rich background in manometric studies as a published literature review (Cock & Omari 2018) and other aspects related to our understanding of swallowing physiology (Omari et al. 2015, Omari et al. 2016, Omari et al. 2016 no. 2, Cock et al. 2016, Cock et al. 2016 no 2, Leibbrandt et al. 2016, Cock et al. 2017, Cock & Omari 2017, Doeltgen et al. 2017, Cock et al. 2020, Omari et al. 2021), this thesis presents the findings of studies exploring *normal* swallowing function in ageing within both the pharyngo-upper oesophageal sphincter (pharyngo-UOS) (Part II, chapters 5,8), oesophageal and oesophago-gastric junction (including lower oesophageal sphincter - LOS) regions (Part II, chapters 6-8), before assessing symptomatic patients suspected of having both oropharyngeal (Part III, Ch 9) or oesophageal symptoms (Part III, chapters 10,11). Following this, in Part IV the implications of the findings in normality and symptomatic patients are explored.

It is beyond the scope of this thesis to provide a full exploration of the technical aspects of, or triangulation against, existing assessment methodologies, such as electromyographic recordings of muscle function or radiology. To this end, I travelled to Madison, Wisconsin and collaborated with colleagues in Leuven, Belgium and Sydney, Australia, but also locally in Adelaide, Australia, to assess technical aspects and triangulate manometry data with electromyography and radiology. These experiments provide some background for the work presented in this thesis and, where published, have been included in the appendices. I am grateful towards and have benefitted from the mastery and multiple additional explorations of my colleagues and co-students in this regard, which equally contributed to furthering our understanding of swallowing function across the lifespan and which have enriched the work presented in this thesis. It is my vision that this work provides the foundation upon which future work can be based to translate such understanding into improving functional outcomes for older persons with impaired swallowing function to ensure not only better health, but also better quality of life and the ability "*to be and do what they have reason to value*".

Chapter 2 Literature Review

> *"What has not been examined impartially, has not been well examined. Skepticism is therefore the first step towards truth."* - Denis Diderot, Philosopher

This literature review consists of three parts:

2.1 Functional anatomy and physiology of swallowing

2.2 Defining function and dysfunction in older persons

2.3 Systematic review of manometry and impedance in older persons (published)

Chapter 2.1 The functional anatomy of swallowing

Despite the essence and apparent simplicity of movement of food or fluids from the mouth to the stomach and onwards for digestion and absorption while maintaining airway defense, ingestion through swallowing is a complex physiological function. There are several reasons for this; i. the airway and food pathways cross over in the pharynx (Matsuo & Palmer 2008); ii. there is a rich and complex interplay between neuromuscular reflex mechanisms involved in swallowing and other physiological processes such as airway protective mechanisms (Matsuo & Palmer 2008, Costa & Lemme 2010, Sasegbon & Hamdy 2017); and iii. the swallowing system has to adapt to swallow boluses of differing sizes and consistencies (Cook et al. 1989, Clavé et al. 2006, Clavé et al. 2008, Cock et al. 2017, Ferris et al. 2021).

Swallowing function is best considered as a single physiological system with multiple interconnected and interrelated components. Traditional models have divided the swallowing task into different phases based on the anatomical location of the bolus (Matsuo & Palmer 2008) (Table 2.1). The oral phase may also be subdivided into preparatory and transfer oral phases (Matsuo & Palmer 2008), leading to a *four-phase model* (Table 2.1), while the preparatory phase is also sometimes regarded separately (Dodds et al. 1990; Dodds et al.

1990 no 2). During solid bolus formation, the oral preparatory and transfer phases overlap so that the four-phase model does not adequately describe solid eating (Palmer et al. 1992). To further confuse matters, the terminology *swallowing phases* or *stages* are, at times, used interchangeably (Goyal and Mashimo 2006) and functional overlap varies on what exactly is meant by each term (Table 2.1).

Table 2.1 Stages/Phases of Swallowing

Anatomical Phases/Stages	Four Phase Model	Purpose
1. Oral	1. Preparatory/Mastication 2. Transfer	1. Bolus Preparation 2. Bolus Transfer
2. Pharyngeal	3. Pharyngeal	3. Bolus Transport
3 Oesophageal	4. Oesophageal	

For this thesis, the anatomical local of the bolus will be used to describe swallowing phases, and the focus is on involuntary or transport functions (Table 2.1). This does not diminish the critical importance of the oral phase, which is included in its contribution to measurably progress the swallow before and during the triggering of pharyngeal contraction.

Although such models simplify the understanding of swallowing for scholars, there are some fundamental issues by dividing swallowing in this way. Division simply by anatomical regions is an oversimplification, which fails to acknowledge the important influence of central nervous system or neurohumoral factors, distracts from components not specifically mentioned as parts of, and most importantly, has facilitated study of different anatomical components by different subject specialists (e.g. swallowing speech pathologists, ear, nose and throat

specialists, gastroenterologists and gastrointestinal surgeons) as separate functional units without recognising or appropriately acknowledging the interdependence of such units.

In my view, the separate study of oropharyngeal and oesophageal swallowing has much to do with the use of anatomical regions in descriptions of swallowing phases. An almost complete absence of studies relating to the proximal oesophagus may be due to the absence of this anatomically and functionally different region from the classification of oesophageal motility disorders, which only considers the distal oesophagus (Pandolfino et al. 2009, Bredenoord et al. 2012, Kahrilas et al. 2015, Yadlapati et al. 2021). Abnormal function affecting the proximal oesophagus has been under recognised and therefore poorly considered.

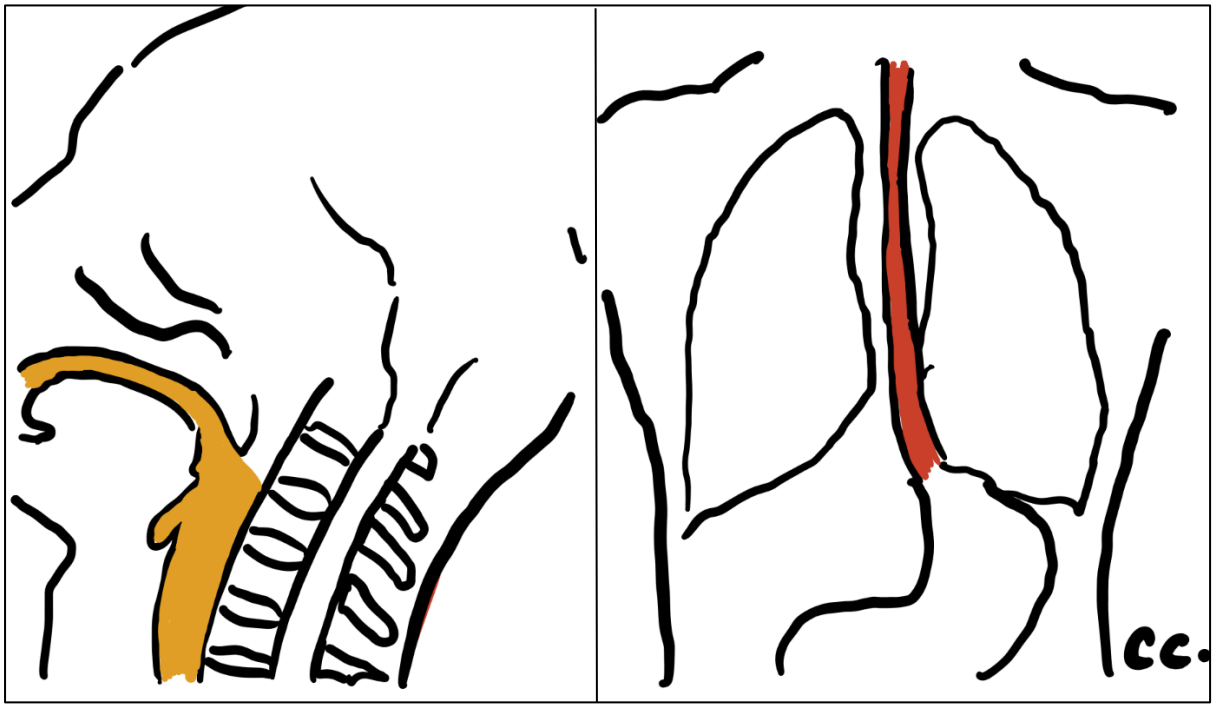

Figure 2.1 The *division* between oropharyngeal (orange) and oesophageal (red) swallowing (own artwork by candidate)

2.1.1 Central nervous system

Central inputs into swallowing function are critical, a fact which becomes even more apparent with the interruption of such mechanisms during disease processes such as cortical stroke

(Michou & Hamdy 2009, Vasant & Hamdy 2013, Wilmskoetter et al. 2020). The oral phases of swallowing are under conscious control, while the pharyngeal and oesophageal phases result from a reflexive, brainstem-based swallow response (Jean 1984, Jean 2001). We can measure the biomechanics of the reflexive components of the swallowing response using methods such as manometry with impedance.

Central motor control of swallowing develops during childhood (Ludlow 2015) prior to which all swallowing occurs reflexively (Lau 2015, Rommel et al. 2011). Miller originally described a role for the central nervous system in swallowing in the early part of the twentieth century while studying cats (Miller 1916). During further animal experiments, Penfield and Rasmussen identified a motor area in the lateral primary motor cortex which, when electrically stimulated, produced a swallowing motor response (Penfield & Rasmussen 1950). This motor area for swallowing involves the *M1* facial motor cortex and adjacent areas controlling facial, laryngeal pharyngeal muscle groups (Martin et al. 1999). Studies furthermore showed the swallowing area to be present in both cerebral hemispheres (Ludlow 2015). Animal studies and imaging also suggest areas in a premotor context, supplementary motor cortex and elsewhere may also be involved in swallowing function (Martin et al. 1999, Martin et al. 2001). Cortical activation occurs for and is different for both voluntary and involuntary (reflexive) swallowing (Martin 2001) and even though represented in both cerebral hemispheres, activation occurs much more prominently in one over the other – Figure 2.2 (Martin et al. 2001, Martin et al. 2004, Furlong et al. 2004).

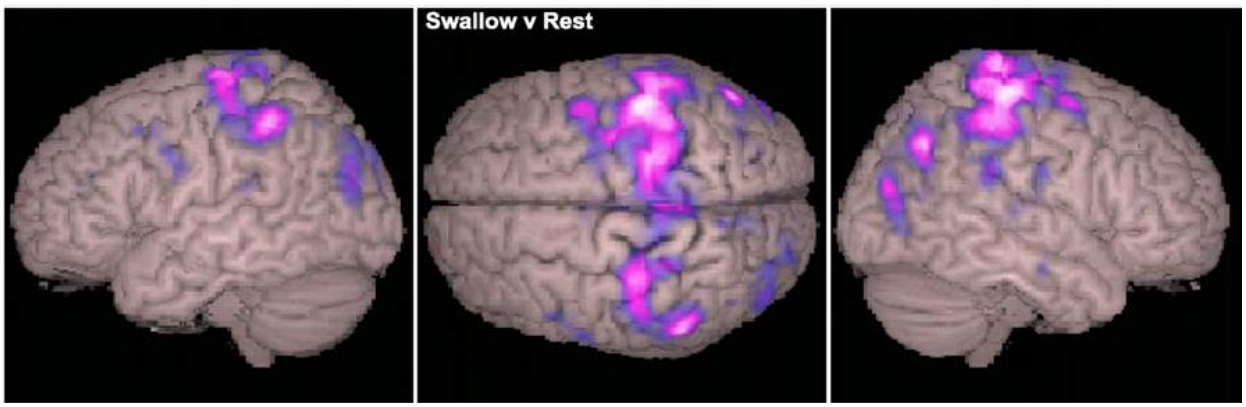

Figure 2.2 Bilateral cortical activation during swallowing (Furlong 2004, used with permission from publisher).

Studies using brain stimulation demonstrate neuroplasticity and adaptive swallowing behaviors. Central processing of sensory stimuli may interact with and influence motor cortex outputs and is measurable as changes in swallowing biomechanics (Doeltgen et al. 2018). Using functional MRI, Humbert et al. (Humbert et al. 2009) demonstrated increased cortical activity in older, as compared to younger individuals, while swallowing. Brain activity also increased with increasing bolus consistency (Humbert et al. 2009). The interpretation of these findings was that with accumulating swallowing challenge related to bolus or with biomechanically more challenging swallowing in age, cortical activation increases as an adaptive mechanism.

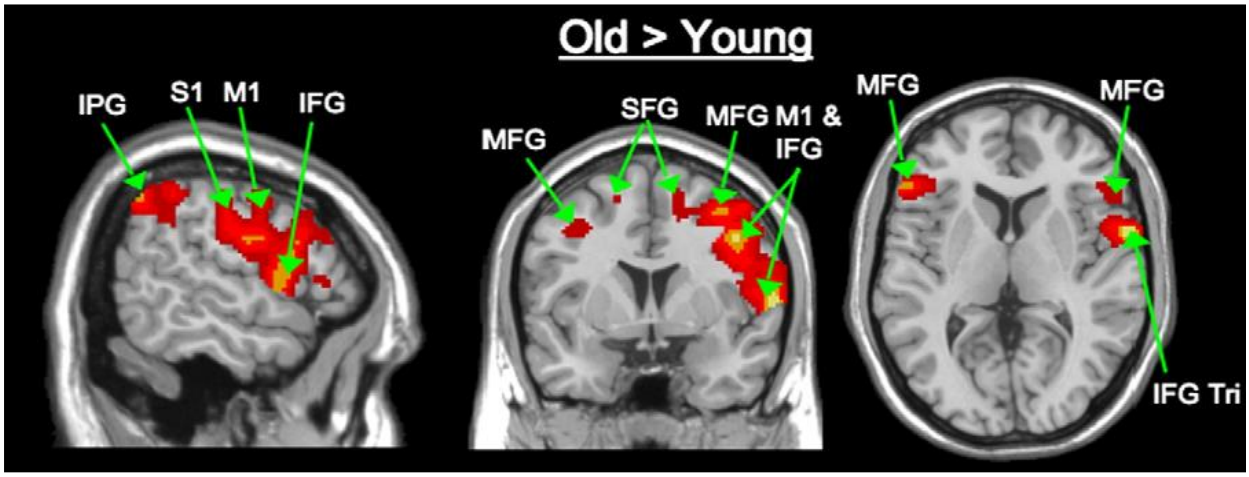

Figure 2.3 Increased brain activation in older vs younger individuals during swallowing (Humbert et al. 2009) (used with permission from publisher).

There may be multiple additional under-recognised cerebral functions related to swallowing function. In older persons the influence of mood, social isolation, decreased taste, neurodegeneration and accumulated neural deficits may influence appetite, food preparation and eating behaviour. Impairments of these aspects may be superimposed on subclinical swallowing disorders, worsening the risk of malnutrition and its consequences.

2.1.2. Brainstem

The brainstem central pattern generator (GPG) is the control center of the swallowing motor plan (Jean 1984, Jean 2001, Lang 2009) and comprises groups of neurons, receiving cortical but also peripheral neural inputs, with outputs to the premotor and motor neurons involved in swallowing. Figure 2.4 is a schematic representation of the organisation of brainstem-based swallowing.

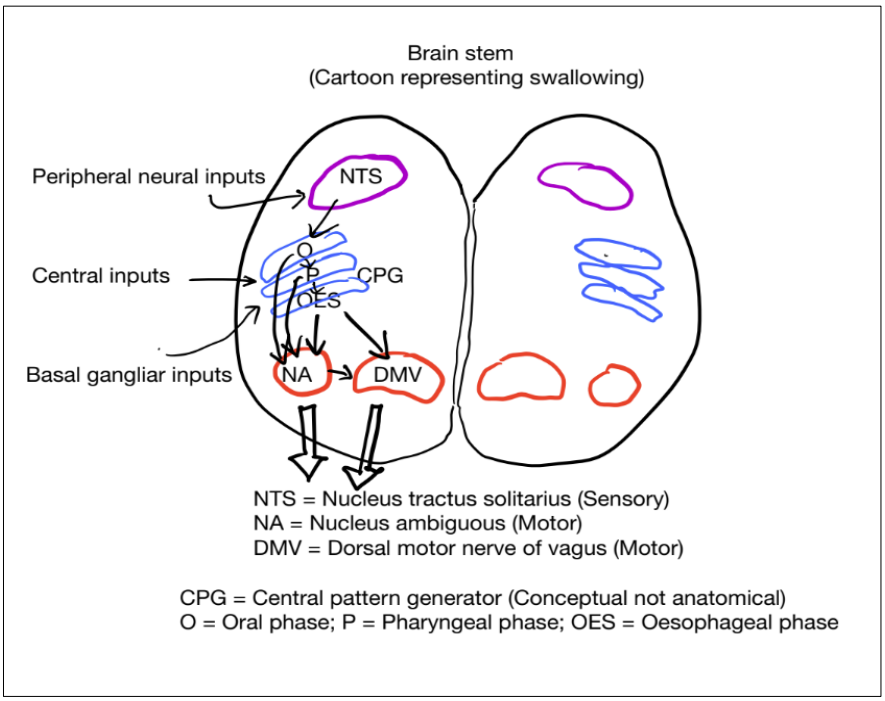

Figure 2.4 Brainstem model of the swallowing central pattern generator (CPG) - blue. Some models would have it that the CPG consists of separate oral, pharyngeal, and oesophageal components. Swallow initiation can occur at any point within the CPG, but all subsequent phases follow in sequence. E.g., pharyngeal and then oesophageal phases can occur without preceding oral phase, and oesophageal phase can occur without oral or pharyngeal phases but once the sequence is triggered, unless inhibited within the CPG, as for multiple swallows, will always progress in sequence (Authors own).

The different phases of swallowing are coupled to the brainstem CPG. Another way of conceptualising this would be to say that each anatomical phase has its own CPG and that these are interconnected via inhibitory and excitatory neural pathways. The concept of inhibition and excitation is very important in terms of understanding swallowing behaviour – for the reflex swallow pathway inhibition always precedes excitation which allows for bolus accommodation, followed by muscle contraction leading to bolus clearance. This process needs to be coordinated with sphincter relaxation, opening and closure. This coordination is

choreographed within the brainstem. For the distal oesophagus, initiation of primary peristalsis occurs in the brainstem, with further modulation of peristalsis possible via activation of peripheral nervous system circuits.

2.1.3 Oral phase of swallowing and tongue function

Bolus preparation occurs during the first part of the oral phase of swallowing through mastication, salivary mixing and bolus aggregation (Matsuo & Palmer 2008). The importance of intact dentition, particularly as relates to swallowing increased consistency boluses in older individuals cannot be overstated (Matsuo & Palmer 2008, Furata & Yamashita 2013). Adequate production of saliva is another factor which is particularly relevant to ageing as, not only does saliva production decrease, but older patients are often on medications, such as anti-depressants or antipsychotics, with anticholinergic side-effects, one of which is decreased saliva production which may influence bolus preparation (Matsuo & Palmer 2008, Yamaguchi et al. 2019). Conditions such as Sjögren's syndrome should also be considered.

Oral transit time is increased (takes longer) as bolus consistency increases (Dantas et al. 1990). For patients with swallowing impairments, consumption of a bolus that does not flow readily allows for better tongue-based control of swallowing function (Clavé et al. 2006) and is helpful for delaying the time required for trigger of the pharyngeal phase of swallowing, thereby allowing for the recruitment of more sensor motor units to better modulate an appropriate swallow motor response.

Two types of tongue movement, namely the *dipper* and *tipper/ incisor* swallow have been described but essentially the dipper type scoops the bolus into an identical starting position with the tongue tip positioned at the incisors (Cook et al. 1989, Dantas et al. 1990, Dodds et al. 1990, Dodds et al. 1990 No 2). Despite subtle differences swallowing liquids or increased

consistencies, the tongue plays a critically important role in bolus control and swallowing initiation (Shaker et al. 1988, Dantas et al.1990).

The prepared bolus is transported to a groove in the posterior tongue (Hamlet et al. 1988). During the final part of volitional swallow initiation, the bolus is propelled postero-inferiorly through the supero-posterior movement of the posterior tongue. This tongue-based movement not only initiates bolus propulsion but also forms a tight seal in the posterior pharynx. These movements are temporally related to and tightly linked to the onset of superior hyoid movement and pharyngeal myoelectric activity (Cook et al. 1989).

DeJeager and colleagues (Dejeager et al. 1997) identified a reduced tongue driving force as one of the important mechanisms involved in increased pharyngeal bolus retention in older persons. Importantly in this context residue had previously been demonstrated in populations of non-dysphagic (i.e., asymptomatic) older persons (Ekberg & Feinberg 1991, Cook et al. 1994).

Some of the most interesting historical papers on swallowing function assessed radiological oesophageal bolus clearance in patients after resections of either the anterior or posterior tongue. While patients were able to compensate even for resection of the entire anterior tongue, posterior tongue resections profoundly affected their ability to radiologically clear bolus (Hirano et al. 1992). Despite these compelling findings, which explains swallowing difficulties or dysphagia in many patients and serves as a reminder of the importance of posterior tongue function, the importance of tongue-based propulsion on oesophageal clearance has not been critically re-assessed and, as tongue weakness occurs in association with dysphagia symptoms in healthy ageing (Lawson et al. 2017), is especially relevant to an older population with sarcopenia (Chen et al. 2021, Shimizu et al. 2021).

2.1.4 Pharyngeal anatomy and the pharyngeal pump mechanism

The pharynx forms the posterior space behind the nasal and oral cavities, and inferiorly is located posterior to the larynx and continuous with the oesophagus. The two main functions are transport of food/ fluids and airflow (Jones 2006, Dodds et al. 1990, Matsuo & Palmer 2009). Functionally we need to consider the pharyngeal lumen, pharyngeal walls, and interaction of the pharynx with surrounding structures such as the palate and larynx. The pharyngeal lumen is important to the understanding of the radiology of oropharyngeal swallowing and is commonly divided into the nasopharynx, velopharyngeal space, mesopharynx, and hypopharynx (also see figure 2.1.5). The pharyngeal walls have multiple constituents: soft tissue, vasculature, connective tissue, fascia, nerve tissue, including the pharyngeal plexus and pharyngeal muscles (Jones 2006, Dodds et al. 1990). The upper oesophageal sphincter within the pharyngoesophageal segment will be considered separately (Cook et al. 1989).

The pharyngeal lumen forms a pharyngeal chamber during swallowing (Sia et al. 2018). Due to the crossover of air and food (see more below under airway protective mechanisms) luminal configuration is critically important and pressure phenomena within the pharyngeal chamber direct and propel swallowed boluses and air content. The pharyngeal chamber is sealed by four soft tissue structures acting as valves: the tongue anteriorly (oral cavity), the soft palate (nasopharynx), laryngeal closing apparatus (laryngeal introitus) and the upper oesophageal sphincter – UOS (oesophagus) (Sia et al. 2018).

The pharynx has two muscle layers: an internal longitudinal and external horizontally orientated muscle layer (of note these layers occur in reverse configuration in the oesophagus). The longitudinal muscles are the palatopharyngeus, stylopharyngeus and salpingopharyngeus muscles. Contraction of the pharyngeal longitudinal muscles leads to shortening of the pharynx, which provides a mechanical advantage for transport through the

pharyngeal lumen. The circular muscles are the superior, middle, and inferior pharyngeal constrictor muscles (Bui & Das 2021) (SPC, MPC, IPC in figure 2.5).

The pharynx normally contracts in a well-orchestrated manner and acts in concert with the posterior tongue to form the *pharyngeal pump* mechanism (Bupthpitiya et al. 1987, Bardan et al. 1997, DeJeager et al. 1997). During swallowing, the pharyngeal chamber seals completely and pressure builds up within the chamber via a piston-like action of the posterior tongue and is released via opening of the UOS (Sia et al. 2018). These actions forcefully propel the bolus down the oesophagus (Bupthpitiya et al. 1987). The trajectory of the bolus head into the oesophagus and its impact on oesophageal contraction can be tracked during impedance manometry using pressure-flow analysis as a demonstration of this phenomenon (Omari et al. 2012).

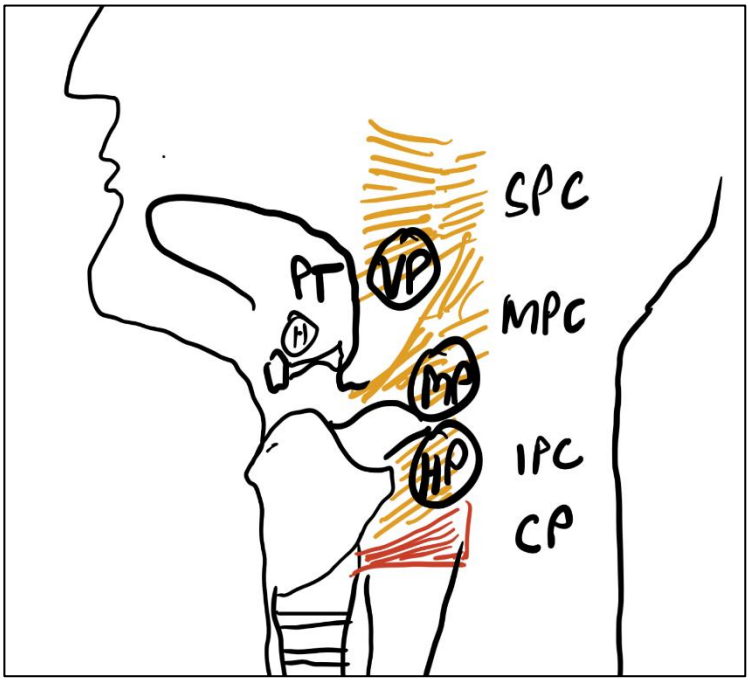

Figure 2.5 The pharynx with the velopharynx, mesopharynx and hypopharynx. The circular musculature of the pharynx consists of the superior (SPC), middle (MPC) and inferior pharyngeal constrictors (IPC). The upper oesophageal sphincter is formed by primarily the cricopharyngeus, (CP) with contributions from the IPC and superior oesophageal circular muscle fibers. (*Authors own*)

2.1.5 Upper Oesophageal Sphincter (UOS/UES)

The UOS is a muscle structure with barrier function in the pharyngoesophageal segment. The cricopharyngeus (CP) muscle, a sling extending posteriorly from the cricoid cartilage forms the majority of the UOS, with contributions from the inferior pharyngeal constrictor and upper oesophageal circular muscle (Figure 2.5) (Kahrilas et al. 1988, Lang & Shaker 1997, Sivarao & Goyal 2000). The CP has constant brainstem based neural input leading to tonic contraction as its resting state. Relaxation occurs following neural deactivation (Cook et al. 1989).

The tonically contracted CP acts as a defense mechanism to prevent retrograde aspiration and swallowing of air (Creamer & Schelgel 1957, Enzmann et al 1977, Gerhardt et al. 1978). Several unique properties of the CP enhance its ability for prolonged tonic contraction. The CP contains more elastic connective tissue when compared to other skeletal muscles within the same individual (Bonington et al. 1988, Kristmundsdottir et al. 1990), and it consists of a large proportion (85%) type I slow twitch muscle fibers (comparatively the quadriceps has 41%) (Bonington et al.1988). A high content of elastic tissue allows generation of maximal active tension in the UOS at nearly twice its resting length. The inferior pharyngeal constrictor has two components with the upper component similar to other skeletal muscles, while the most inferior portion has similar features to the CP (Mu & Sanders 2001). With increasing age, both elastic tissue and muscle fibers in the CP may be replaced with fibrofatty tissue decreasing sphincter distensibility and increasing the risk of associated diverticulum (Cook et al. 1992). The prominent CP bar seen on lateral swallowing radiology (more below) in some older individuals are thought to relate to a non-relaxing CP muscle, however the origin and significance of this finding remains unclear (Cook et al. 1993, Cook 2011, Allen 2016). While closure of the UOS is important, its opening function is complex, interesting and important, best described by Cook et al. (Cook et al. 1989).

There are multiple contributions to UOS opening: 1. neural deactivation and consequent cricopharyngeal relaxation; 2. hyolaryngeal elevation due to contraction of submandibular muscles pulling the hyoid bone superiorly and anteriorly leading to distraction of the cricopharyngeus 3. Increased intrabolus pressure upstream forcing open the distracted UOS; 4 volume-based modulation of the swallowing response through sensory feedback leading to earlier and greater UOS opening for larger boluses (Cook et al. 1989).

Fibrotic changes in the cricopharyngeus muscle in older person may predispose to the formation of Zenker's diverticulum which may further impact of swallowing changes in this population (Cook et al 1992).

2.1.6 The Oesophageal Body

The oesophageal body can be described as an expandable muscular tube (seen in cross section in figure 2.6), which forms a conduit between the pharynx and the stomach. Its functions are distal transport of food and fluid via peristalsis, proximal transit during vomiting, and oesophageal clearance of chemically active refluxate, containing acid and pepsin (Lamb & Griffin 2005). Sphincter functions, at both the proximal and distal ends of the oesophagus, act in concert with the oesophageal body to prevent reflux and aspiration but here are described separately.

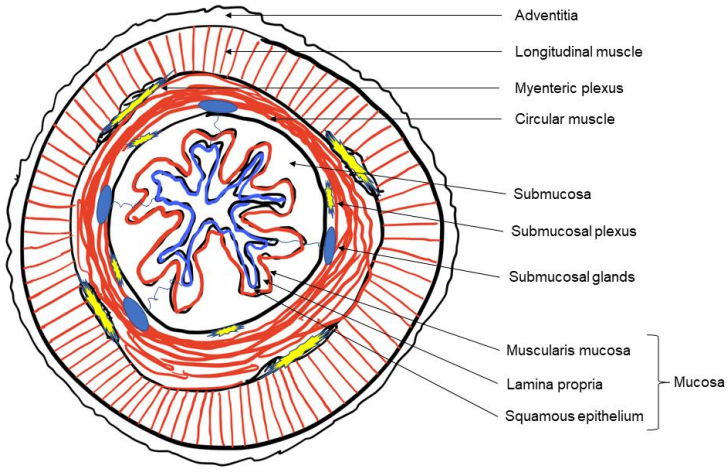

Figure 2.6 Histological cross-section of the oesophageal wall in the resting state. (Own)

Both inhibition and excitation (in that order) of oesophageal muscle layers are important for transport of boluses (Sifrim et al. 1992, Goyal & Chaudhury 2008, Mittal 2011, Lin 2014). Primary peristalsis occurs following swallowing, but the oesophagus also has the ability to contract with distention-based secondary peristalsis in order to clear retained bolus material (Paterson et al. 1991). Tertiary or incoordinate contractions of the oesophageal body are observed as a radiological phenomenon, non-functional and appear to occur more frequently with ageing (Soergel et al. 1964, Zboralske et al. 1964, Stiennon 1968). The manometric correlate of tertiary contractions remains unclear (Triadafilopoulos & Castillo 1991, Mittal 2011, Halland 2016).

The oesophageal body in humans consists of a striated muscle proximal and smooth muscle distal oesophagus with a mixed transition zone in between. In an autopsy study, the overall length of the oesophagus was approximately 23cm in humans with the proximal 4.1-5.6% purely striated, a variable length transition zone (mixed striated/smooth muscle), and 54-62% purely smooth muscle distal oesophagus. The 50/50 split between striated and smooth muscle occurred at 4.7±0.6cm from the cricopharyngeus muscle (Meyer et al. 1986), which can be regarded as mid-point of the transition zone (also see Figure 2.7). Recent data suggests the measured length of proximal contractility in the human oesophagus on high-resolution manometry was 5.1±0.3cm and that intact proximal contraction contributes to successful oesophageal bolus clearance (Jehangir et al. 2020). The difference in measured length of purely striated muscle and what is measured as proximal contraction implies the majority of the measured proximal region consists of mixed muscle fibers. The functional behaviour of these oesophageal regions is different based on underlying anatomical and physiological differences.

In addition to the very important muscle components of the oesophageal wall, there are additional structural elements, such as type I and II collagen, arranged in a crisscross pattern in the submucosa in two helixes spiraling around the oesophagus in opposite directions (Zifan

2017). The mechanical properties and resulting stress-strain behaviour of the oesophageal wall has been studied and is highly relevant to the action of the oesophageal body in response to motor function, and trans-sphincteric bolus movement (Ren et al. 1993, Nicosia & Brasseur 2002, Yang et al. 2006, Vegesna et al. 2012, Mittal et al. 2017, Zifan et al. 2017). Gregerson has demonstrated increased oesophageal wall stiffness with increasing age (Gregerson 2008).

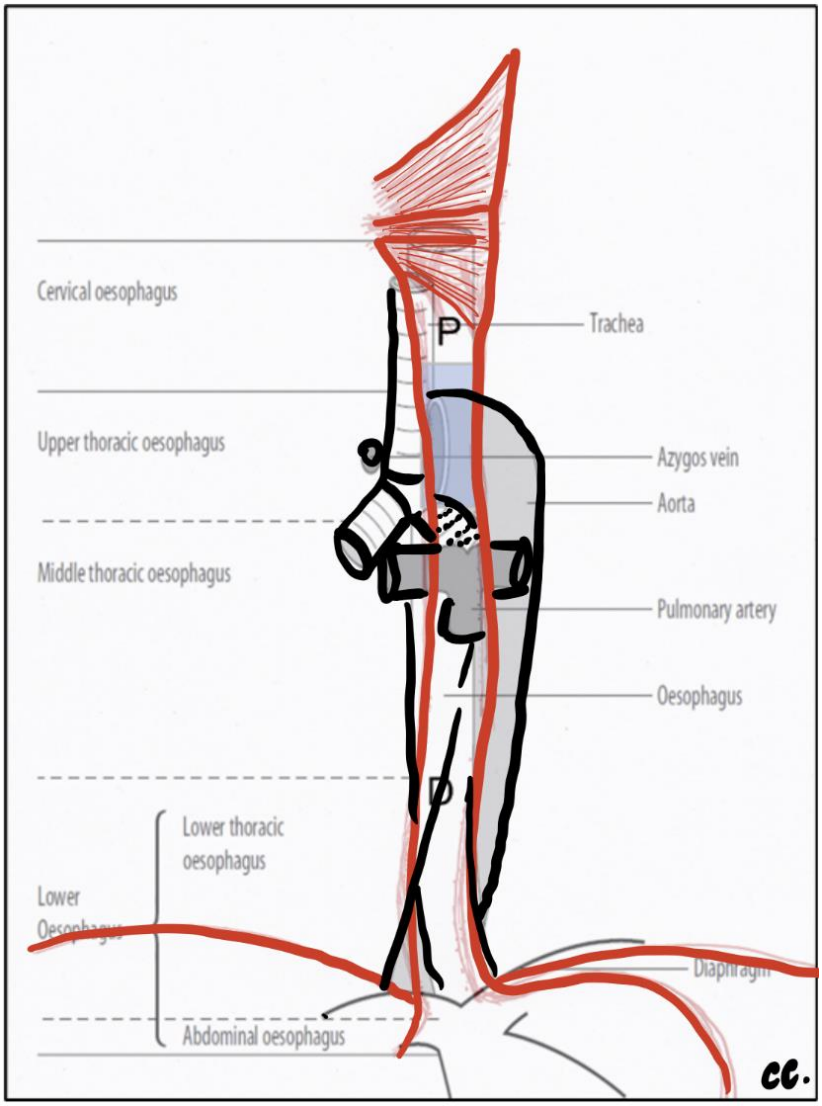

Figure 2.7

Anatomical relationships of the oesophagus. The striated muscle proximal (P) and smooth muscle distal (D) oesophagus is illustrated with overlap of muscle fibers in the transition zone (blue box).

Candidates own illustration combined with figure from Lamb and Griffin *"The Anatomy and Physiology of the Oesophagus"* in Fielding & Hallissey Upper Gastrointestinal Surgery, Springer, 2005 (used with permission)

2.1.6.1 Proximal Oesophagus

The proximal oesophagus consists of striated muscle with motor inputs originating in the brainstem (nucleus ambiguous) travelling within the vagus nerve and synapsing directly on

the muscle end plates via nicotinic receptors (Christensen 1975). The proximal, like the distal oesophagus consists of an inner circular and outer longitudinal muscle layers. The motor nucleus for the proximal oesophagus is the nucleus ambiguous. There are published data, including in humans, suggesting the proximal oesophageal region is more sensitive, in terms of conscious awareness, to sensory stimuli such as distention, as compared to the distal oesophagus (Patel & Rao 1998, Woodland et al. 2015, Cock et al. 2020). With increased motor stimuli, contractile latencies decreased in the proximal oesophagus, in contrast with increasing distally (Crist et al. 1984). These effects are lost under the influence of atropine (i.e., with the loss of cholinergic response). (Crist et al. 1984).

Overall, the sensorimotor behaviour of the proximal oesophagus as relates to oesophageal symptoms and high-resolution manometry is incompletely understood due to a relative paucity of data, as it does not form part of the classification of oesophageal motor disorders (Pandolfino et al. 2009, Bredenoord et al. 2012, Kahrilas et al. 2015, Yadlapati et al. 2021), and is thus rarely interpreted by gastroenterologists and also is beyond the region of most interest to ear, nose and throat specialists and swallowing speech pathologists, who are mainly interested in oropharyngeal swallowing and UOS function. The thinking is that the increased proximal oesophageal sensitivity has a protective role to avoid swallowing with pre-existing bolus residue, a physiologically potentially dangerous behaviour (Woodland et al. 2015, Cock et al. 2020), however, this sensitivity decreases with ageing so that UOS contractile reflexes and secondary peristalsis reduce (Ren et al.1995, Mei et al. 2018).

What we do know of the proximal oesophagus is that its motor function appears to be separate from that of the distal oesophagus, so that when studying peristaltic contractility reference is made to *separate contraction waves above and below the transition zone* (Ghosh et al. 2006). Preceding peristaltic contraction, deglutitive inhibition in the proximal oesophagus is important to the accommodation phase of oesophageal bolus transport (Lin et al. 2014). Proximal deglutitive inhibition must be brainstem based. Even if proximal oesophageal motor behaviour

is initiated differently from distal contractions, there is a close interrelationship between proximal and distal contractility. Few data describe the function of the proximal oesophagus. Dantas et al. (Dantas et al. 2010) limited their description of proximal motor function to a few healthy volunteers aged 60 to 74 years of age and demonstrated somewhat delayed contractions of a shorter duration in the oldest compared to the youngest group (18-30 years of age) studied. Contractile amplitude and overall area under the curve, were similar in the oldest subjects. These data are in keeping with that of Nativ-Zeltzer (Nativ-Zeltzer 2016), which showed no differences in the proximal oesophagus of aged subjects, (60 to 80 years of age), as compared to those aged 21-40 years. There appears to be a complete absence of literature describing the proximal oesophagus in the older old.

2.1.6.2 Distal Oesophagus

The distal oesophagus consists of smooth muscle. Like in the proximal oesophagus, contraction is preceded by inhibition and relaxation which is critical for normal function (Lamb & Griffin 2005, Sifrim & Jafari 2012, Miller et al. 2013). Distal oesophageal motor function is best considered as occurring indirectly, meaning the motor outputs from the dorsal motor nucleus of vagus synapse on interneurons in the intermuscular myenteric plexus, with secondary order neurons to circular muscles. Motor inhibition occurs via nitric oxide and precedes motor excitation through cholinergic mechanisms (Figure 2.8).

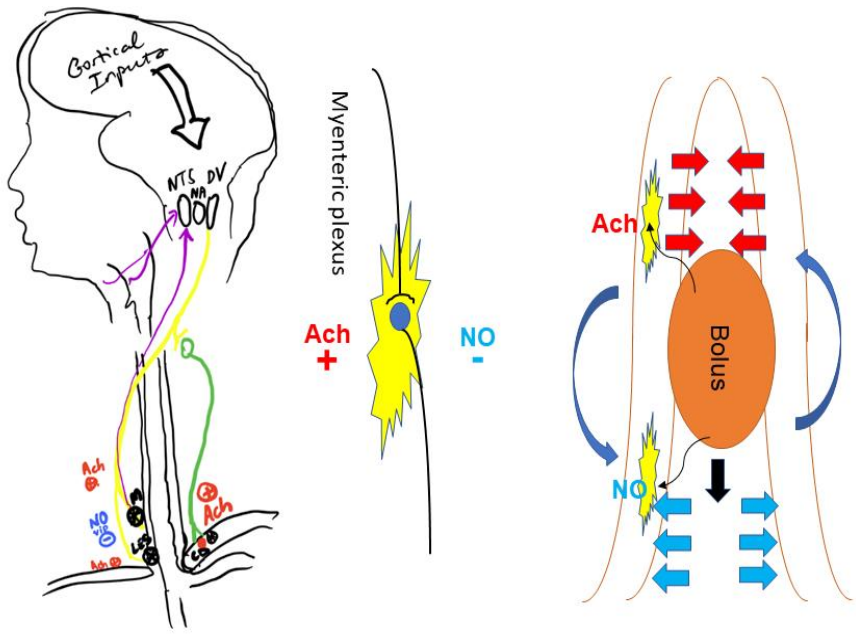

Figure 2.8 Neural inputs into the oesophageal body and lower oesophageal sphincter relaxation. Vagal inputs lead to inhibition through nitric oxide (NO) and vasoactive intestinal peptide (VIP) and excitation through cholinergic mechanisms (Ach) after synapsing in the myenteric plexus. The neuromechanical loop hypothesis (Costa et al 2015; Spencer et al. 2016) determines that bolus in the oesophageal body induce inhibition ahead of, and excitation behind the bolus to promote bolus transport – with the cycle repeating (the so-called neuromechanical loop) at a point more distally

both ahead of and behind the bolus. Ahead of the bolus, inhibition is induced leading to relaxation and bolus accommodation. Simultaneously behind the bolus contractions are stimulated through cholinergic mechanisms leading to bolus propulsion. The process then recurs after a more distal segment is distended, through a neuro-mechanical loop mechanism (Figure 2.8). The concept is not novel and is a variant of the very familiar Starling mechanism (Costa et al. 2013, Spencer et al. 2016).

Our current understanding is that there is a graduated increase in inhibitory neurons from proximal to distal, while at the same time there is a graduated decrease in cholinergic neurons (figure 2.9, Crist et al. 1984). Alternatively, the quantum of neurotransmitter released may differ between proximal and distal oesophageal regions. Regardless of the underlying mechanism, the gradient created towards the most distal oesophagus, in part, accounts for an increasing latency from swallow onset to contraction as we move more distally down the oesophagus (Sifrim et al. 1992, Sifrim & Jafari 2012).

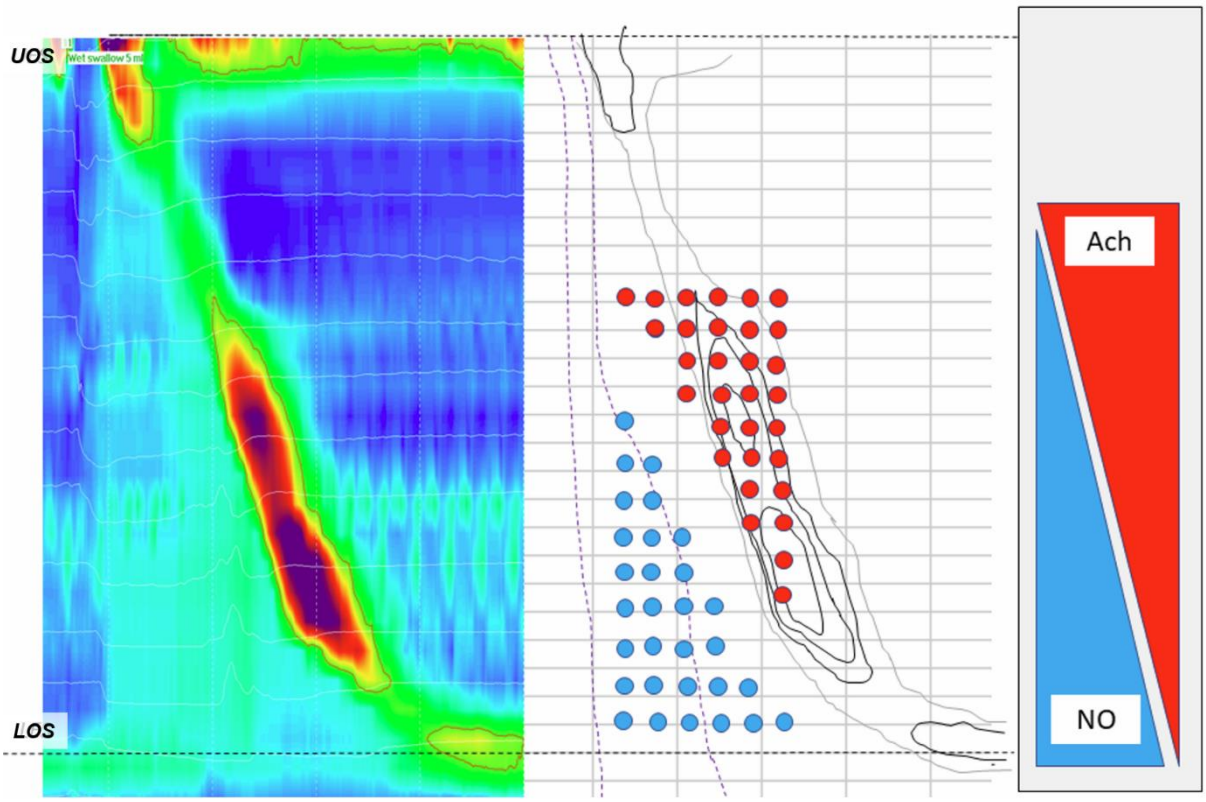

Figure 2.9 Oesophageal pressure topography with overlay of cholinergic (red) and nitrergic (blue) neurons indicating a reducing density of cholinergic from proximal to distal; increasing density of nitrergic from proximal to distal oesophagus (Own).

Mittal and colleagues described, using experiments with intraluminal pressure and ultrasound also described the fine synchrony of circular and longitudinal muscle during oesophageal peristalsis (Mittal 2005), and furthermore its importance in successful bolus passage, and possible role in the genesis of oesophageal symptoms for example in some subtypes of achalasia or spastic motility disorders (Mittal et al. 2006, Mittal 2016). Longitudinal muscle contraction provides a mechanical advantage for more effectively propulsive circular muscle contraction (Brasseur & Nicosia 2002, Brasseur et al. 2007).

The orientation of the muscle fibers in the distal oesophagus may also influence its function. Whereas the circular muscle fibers are relatively horizontally orientated for the majority of the oesophagus, in the most distal portion these fibers are more obliquely orientated (Zifan et al. 2017). The mechanical consequence of such oblique orientation will be a small degree of oesophageal shortening, which may potentially serve as a final component of oesophageal distraction during lower oesophageal sphincter opening. This component has not been widely explored.

The distal oesophagus has been comprehensively studied and its functions make up the majority of publications related to high-resolution manometry. Surprisingly then, based on the premise that the classification of motor disorders is supposed to reflect motor change in relation to symptoms, that the initial versions of such a classification (Pandolfino et al. 2009, Bredenoord et al. 2012, Kahrilas et al. 2015) have not been shown to correlate with symptoms. It is possible that a neurally-based decrease in distal oesophageal sensory feedback occurs with ageing, similar to that demonstrated in reflux disease (DeVault 2002, Johnson 2004). What is underrecognized and an intriguing possibility for this thesis is that some oesophageal motility disorders may also increase with age, with the potential for such disorders to be underreported by older persons. Another possibility is that undiagnosed reflux disease, other forms of mucosal inflammation, or incoordination between circular and longitudinal muscle layers (Mittal 2016) further contribute to dysmotility in ageing.

Including information from impedance in the form of pressure-flow analysis has been shown in some studies to correlate with symptoms including those generated in healthy volunteers, which almost always relate to swallowing increased consistency boluses (Omari et al. 2013, Cock et al. 2020), but also in the context of anti-reflux surgery with post-operative dysphagia (Myers et al. 2012).

Our current understanding is that age-related oesophageal neurodegeneration preferentially affects excitatory motor function while inhibitory function is spared (Johnson et al. 1998, Cowen et al. 2000, Phillips et al. 2003, Wade & Cohen 2004, Cammileri et al. 2008, Salles 2009). An intriguing recent animal study by Kim et al. (Kim et al. 2017) however also suggested a decline in nitric oxide synthetase producing, i.e., inhibitory, cells and interstitial cell of Cajal with increased age. Their study also showed some structural changes including a decline in longitudinal muscle thickness, while circular muscle volume remained preserved.

2.1.7 Oesophagogastric junction and lower oesophageal sphincter

The lower oesophageal sphincter (LOS) and crural diaphragm act in concert to perform a sphincter function at the lower end of the oesophagus. Within the oesophagastric junction (OGJ) the LOS is sometimes regarded as an internal and the diaphragmatic crura as an external sphincter (Figure 2.9; Mittal 1997, Mittal & Balaban 1997, Mittal & Goyal 2006). The anatomy of the OGJ (figure 2.9) is of great importance in reflux disease and anti-reflux surgery and has been studied in depth. The lower oesophageal sphincter is smooth muscle in continuum with the circular muscle layer in the distal oesophagus. The end-expiratory manometrically recorded pressure is indicative of LOS pressure alone (Mittal et al. 1995).

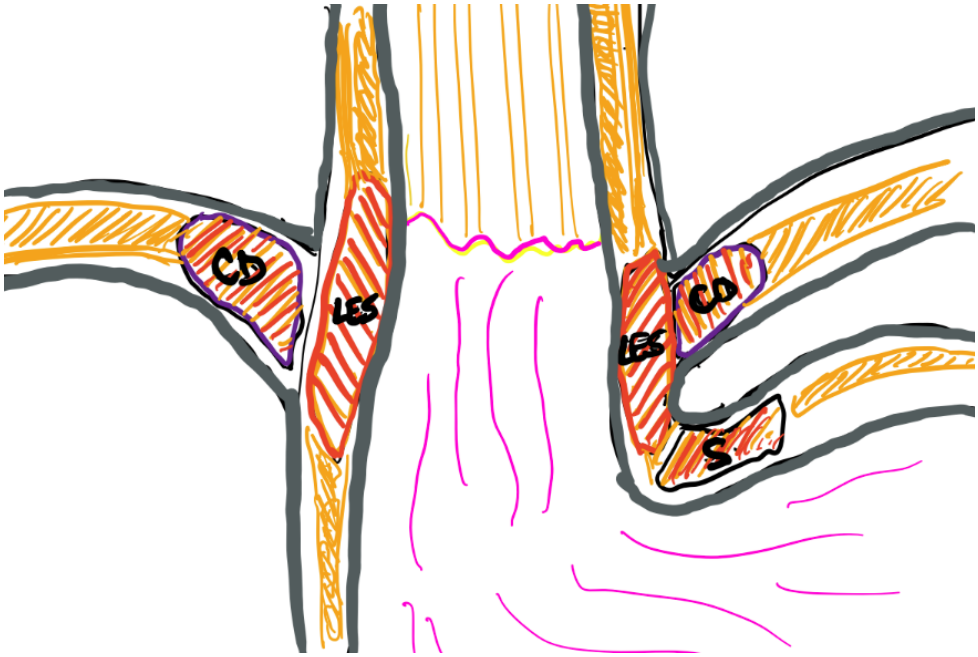

Figure 2.10

The Oesophago gastric junction (OGJ) at the lower end of the oesophagus, consisting of the internal sphincter formed by the lower oesophageal sphincter – LOS, and the external sphincter formed by the crural diaphragm – CD. The sling fibers (S) at the angulus, potentially also contribute to OGJ sphincteric function. (Own)

The LOS maintains a basal tone which prevents free reflux of gastric contents back into the oesophagus. LOS basal tone increases at night. The genesis of LOS basal tone is multifactorial. The majority component of LOS basal tone is myogenic with a minor increase related to central neural inputs (Goyal & Rattan 1978, Mittal & Goyal 2006). In terms of sphincter relaxation, the LOS receives neural inputs from secondary order neurons originating in the distal oesophagus, as well as stretch sensitive neurons in the proximal stomach (Mittal & Goyal 2006).

Inhibitory and excitatory neural fibers to the LOS originate in the dorsal motor nucleus of vagus and receives sensory inputs from the nucleus tractus solitarius and spinal nociceptive nerves (T1-L3). Animal experiments (Yuan et al. 1998, Brookes et al.1996) suggest a further role for bolus-based relaxation of the LOS via release of nitric oxide at the LOS. This mechanism is intrinsic to the peripheral neural system (intramural plexus), and it is likely that it occurs independently of central inputs into LOS relaxation.

In addition to mechanisms leading to relaxation of the internal LOS, such relaxation needs to coordinate with inhibition of crural diaphragm contraction. Mittal et al (Mittal et al. 1987, Mittal et al. 1995) demonstrated that relaxation of the LOS led to inhibition of diaphragmatic contractions but that this action was present to a lesser degree in humans than other animals. It seems likely this reflex action is coordinated in the breathing and swallowing centers in the brainstem, possibly based on sensory feedback via the NTS and with the overriding purpose upper airway protection (see further). Distraction of the OGJ occurs during oesophageal longitudinal muscle and oblique distal circular muscle contraction. Such mechanisms may lead to temporary decoupling of the internal and external sphincters which may allow for final bolus passage at the OGJ.

An increase in intrabolus pressure of at least 20mmHg above baseline is needed to overcome resistance to OGJ bolus flow (Nicosia & Brasseur 2002). A recent description of measurement of OGJ bolus flow during high-resolution impedance manometry studies (Lin et al. 2014) made the assessment of OGJ bolus flow time during pressure-flow analysis an intriguing possibility (see below).

The presence of hiatus hernia is by far the most important anatomical abnormality of the OGJ region, which can be associated with both gastroesophageal reflux disease (Kahrilas 1999) and dysphagia related to mechanical obstruction and/or bolus impaction (Philpott & Sweis 2017). Hiatus hernias (and gastroesophageal reflux) increase with increasing age and also with obesity (Kahrilas 1999). The OGJ region, in particularly the LOS, may also be influenced by several medications, and in many instances use of such medications increase with age and comorbidities.

2.1.8 Mechanisms of airway penetration and pulmonary aspiration

We cannot consider swallowing function without also considering airway protective mechanisms which avoid airway penetration and aspiration. This is due to the cross-over of airflow and food from the oral cavity to the oesophagus within the pharynx. Airway protection is thus an inherent component of pharyngeal swallowing. Airway penetration (either upper or lower) is rare during normal swallowing and represents a form of functional impairment of the pharyngeal swallow.

Table 2.2 provides an overview of the airway protective mechanisms (Pitts 2014). These mechanisms are highly dependent on intact sensory function and beyond the airways also involve mechanisms inherent to swallowing function such a tongue-based bolus control, oro-pharyngeal coordination and upper oesophageal sphincter opening.

Table 2.2 Airway protective mechanisms during swallowing
Coordination of swallowing and breathing
Tongue-based bolus control
Vocal cord adduction
Hyo-laryngeal elevation with: Vocal fold and aryepiglottic folds preventing airway penetration Epiglottis closing laryngeal introitus Upper oesophageal sphincter opening
Cough and cough-swallow coordination

There are three main mechanisms of airway penetration and pulmonary aspiration during swallowing or deglutition, namely pre-deglutitive (Donzelli & Brady 2004, Han et al. 2016), intra-deglutitive (Omari et al. 2011, Molfenter & Steele 2014) and post-deglutitive mechanisms (Molfenter & Steele 2013, Molfenter & Steele 2014). Reflux related aspiration represents a fourth mechanism (Shaker 1995). Multiple airway protective mechanisms need to fail for tracheal aspiration to occur, however, in ageing laryngeal protective reflexes and the ability to accommodate volume is reduced (Dua et al. 2014) so that aspiration risk is greater overall.

Pre-deglutitive penetration, or *premature spill* occurs due to a loss of oral motor control or incoordination of swallowing but is also observed in healthy volunteers. Intra-deglutitive penetration/aspiration occurs when hypopharyngeal intrabolus pressures (increased) exceed the ability of the (weak) pharynx to retain or direct such bolus through the pharyngo-esophageal segment. Reduced upper oesophageal sphincter relaxation, in the presence of intact or reduced pharyngeal contraction, would lead to such increased hypopharyngeal intra bolus pressure and circumstances permissive to *intra-deglutitive aspiration*. There are thus several metrics in concert, or individually which contribute to an increased intra-deglutitive aspiration risk namely pharyngeal weakness (reduced peak pressure, integral), increased intrabolus pressure (IBP in mmHg) (Omari et al. 2011)

Although less recognized as a risk factor for aspiration, recent work by Molfenter et al. have clearly demonstrated the importance of *post-swallow residue* to aspiration on subsequent swallowing (Molfenter & Steele 2013). Specifically, increased consistency residue carries a risk for aspiration of subsequently swallowed liquid content. This potentially makes the often-given advice to follow solids with liquids to aid transit particularly dangerous in the setting of post-deglutitive aspiration risk. The post-deglutitive impedance ratio or a prolonged bolus presence (time) would serve as a marker of this specific risk factor.

Omari et al. (Omari et al. 2011) assessed aspiration events during video-manometry studies (using high-resolution impedance manometry) and found four variables in particular predicted aspiration risk*:

1. Shorter interval between peak distension and contraction;
2. Low pharyngeal peak pressures (low hypopharyngeal peak pressure);
3. Increased pressure at nadir impedance (hypopharyngeal intrabolus pressure);
4. Increased flow interval/ hypopharyngeal bolus presence time.

**See Cock & Omari 2017 for definition and further description*

These four metrics were combined into a single swallow risk index, indicative of increased aspiration risk, as observed on video radiology:

$$\text{Swallow Risk Index (SRI)} = \frac{\text{Bolus Presence Time X IBP}}{\text{Pharyngeal Peak P X (DCL + 1)}} \text{ X } 100$$

This global measure approach has advantages when used for screening purposes. The major disadvantage in the use of SRI is that it's use does not identify the specific mechanism of aspiration but rather contains metrics separately related to pre-, intra-, and post-deglutitive aspiration risk. A more complete understanding of the discreet components may assist in the identification of, and therefore treatments targeting the exact mechanism in individual cases of aspiration. SRI does however provide a biomechanically based impedance manometric target for studies of aspiration in older individuals, for example in those with pneumonias. The hypothesis is that swallowing is impaired below the aspiration threshold in older subjects without and above the threshold with aspiration. If this hypothesis holds it would support the concept of impaired swallowing function reserve in ageing more broadly.

2.1.9 Mechanisms of Oesophageal Bolus Transport

Oesophageal bolus transport occurs during primary peristalsis and describes the process from when the bolus passes through the upper oesophageal sphincter to clearing the

oesophagogastric junction into the stomach. When reflux occurs, or bolus is insufficiently cleared, oesophageal bolus transport can also occur through secondary peristalsis. By implication there are two interrelated clearance mechanisms namely a centrally triggered primary peristaltic and peripherally triggered secondary peristaltic mechanism.

When bolus is introduced into the oesophageal lumen, the oesophagus, during primary peristalsis is in an inhibited state, ready to receive the bolus. This phase is referred to as oesophageal accommodation and is the first of four phases of oesophageal bolus transport, as described by Lin et al. (Lin et al. 2014, See figure 2.11, below).

Following the accommodation phase when the bolus is introduced into the oesophagus through pharyngeal propulsion and with assistance of a short-lasting negative pressurization in the proximal oesophagus (Williams et al. 2001), bolus transport occurs actively through the distal oesophagus and OGJ.

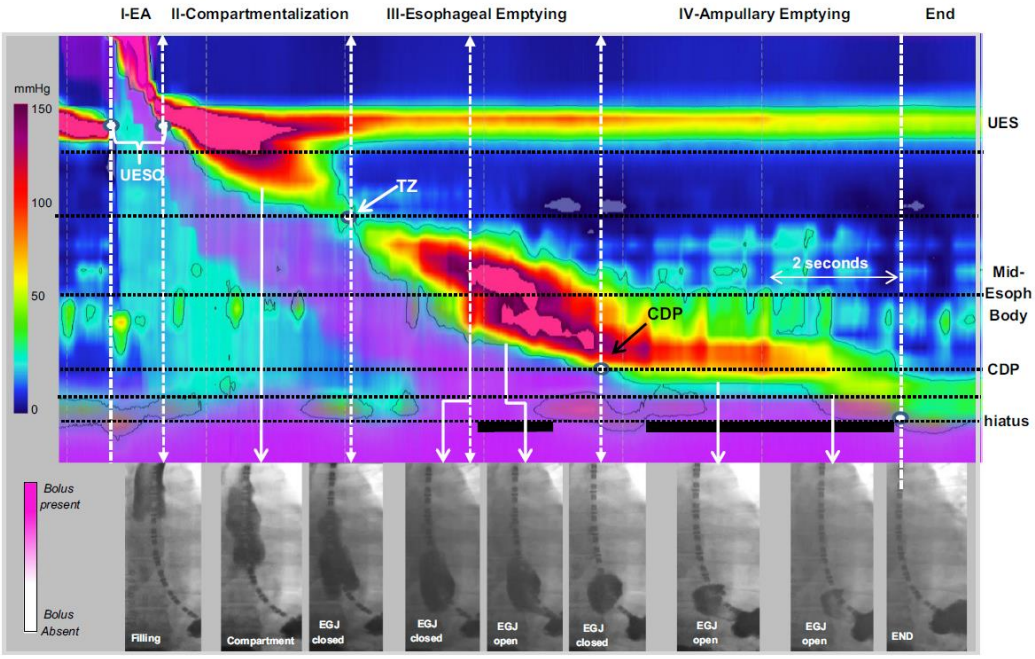

Figure 2.11 The four phases of oesophageal bolus transport (see text) (From Lin 2014, used with permission)

The bolus head distends the distal oesophagus and leads to a *wave of inhibition/distension* travelling ahead of a *wave of contraction* during oesophageal bolus transport (Sifrim et al.

1992, Ghosh 2006, Abrahao et al. 2011). Bolus-based distension provides a feedback loop within the myenteric plexus which causes the oesophagus to relax ahead of and contract behind the bolus (Costa et al. 2013, Leibbrandt et al. 2018). Contraction occurs onto the bolus tail, which through mechanical forces propels the bolus forwards. In the upright position this action is aided by gravity and by implication lesser force are needed to overcome the resistive forces from the oesophageal walls and sphincter mechanism.

The bolus shape changes during oesophageal passage and according to internal consistency; with liquid bolus being more elongated (seen below in Figure 2.12 from Dodds et al. 1972), while a more football-shaped bolus is formed for increased consistency boluses (Mittal et al. 2020, Omari et al. 2022 no 2)

During this compartmentalized phase of bolus transport, the advancing bolus is compressed by the resistive force of an incompletely relaxed LOS. Such compression will cause intrabolus pressures to increase within the compressed bolus and if such an increase exceeds the differential between the oesophageal lumen and intragastric pressure, will aid in clearing the bolus through the OGJ during the next oesophageal emptying phase.

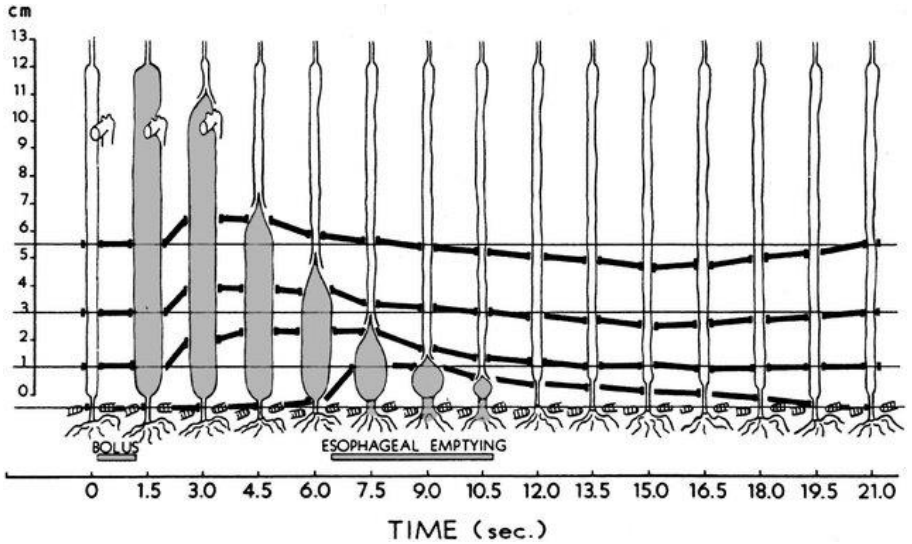

Figure 2.12 Bolus shape during oesophageal bolus transport based on radiology (see text) (From Dodds 1972, used with permission)

Oesophageal emptying is aided by the formation of a phrenic ampulla. This process involves what is interpreted to be the result of longitudinal muscle contraction (observed in figure as

the lowest black line, representing a radiopaque marker, being pulled proximally) (Dodds 1972). Brasseur and Pal (Pal & Brasseur 2002, Brasseur et al. 2007) describe the mechanical advantage provided by longitudinal muscle shortening to oesophageal bolus transport and clearance. Recent work also suggests the spiral formation of especially the most distal circular muscle fibers may contribute to distal oesophageal shortening as the most distal circular muscle fibers are not horizontally but rather tangentially orientated (Mittal et al. 2017, Zifan et al. 2017).

The oesophagogastric junction (OGJ) forms the barrier between the oesophagus and stomach. Brookes also described in animal experiments peripheral NO release as part of the mechanism of LOS relaxation and opening (Brookes et al. 1996). Beyond the lack of structural mechanical obstruction, successful oesophageal bolus transport thus depends on intact inhibition, excitation and normally functioning circular and longitudinal muscle fibers. The final phase of oesophageal bolus transport consists of ampullary emptying, where the remaining ampullary contents are cleared through to the stomach during the reconstitution of the LOS.

During manometry with impedance, the ratio of the impedance at its nadir, which signifies peak luminal distension (Silny et al 1993, Omari et al. 2014, Rommel et al. 2014), to that at peak contraction, representing luminal closure (Omari et al. 2014, Rommel et al. 2014, Leibbrandt et al. 2018) can be measured. This impedance ratio (IR) is a measure of the extent of oesophageal bolus clearance (see methods – chapter 4).

2.1.10 Oesophagogastric reflux and anti-reflux mechanisms

The lower oesophageal sphincter mechanism is a key component of the anti-reflux barrier between the stomach and distal oesophagus. The complex anatomy of this region further enhances the barrier function through the clasp and sling fiber arrangement of muscle fibers at the OGJ (Mittal 1997, Mittal & Balaban 1997, Mittal & Goyal 2006). However, when the

anatomical structure of the OGJ gets disrupted, as with hiatus hernia, some structural components of the anti-reflux barrier is lost (Bredenoord & Smout 2012). Hiatus hernia is associated with higher oesophageal acid exposure, increased prevalence of reflux esophagitis, and more severe esophagitis and symptoms (Bredenoord & Smout 2012). Some studies have shown an increase in HH in older persons (Kahrilas 1999) and furthermore dysphagia in association with HH in such older individuals (Philpott & Sweis 2017).

During manometry, dual high-pressure zones are demonstrated at the oesophago-gastric junction – with the proximal occurring at the anatomical location of the intrinsic LOS, and the second representing the crural diaphragm (Bredenoord & Smout 2012). The relevance of the resting pressure at the OGJ to barrier function remains controversial. Some historical studies showed a lower LOS resting pressure as being associated with increased reflux (Ahtaridis et al. 1981, Kraus et al. 1990) but this had not been demonstrated universally. The transient lower oesophageal sphincter relaxation reflex (TLOSR), which occurs with proximal gastric distension, prevents overdistension of the stomach by air by the belch response (Wyman et al. 1990). TLOSR has been shown to be one of the most important mechanisms of liquid reflux (Holloway et al. 1991).

Reflux of gastric contents is a normal physiological phenomenon which only becomes abnormal when excessive. Oesophageal clearance is an important mechanism in preventing oesophageal reflux disease (Stacher et al. 2006). In conclusion, both sphincter mechanisms and oesophageal clearance are important to prevent pathological reflux.

Older patients with reflux may not be as readily investigated (DeVault 2002). The prevalence of reflux disease does not appear to alter much throughout the lifespan, but reflux is often asymptomatic in older patients, despite more severe oesophagitis and a greater proportion of reflux-related complications in older persons (Collen at al 1995, El-Serag & Sonnenberg 1997, Zimmerman et al 1997, Johnson 2004).

Chapter 2.2 Defining function and dysfunction in older persons

A primary purpose of this research program was to determine normal swallowing function in older persons. In the context of this thesis, I will refer to four over-arching representations of *normal function*, described in more detail below:

1. Normal function, as measured against a young, healthy population;
2. Normal function, as measured against an age-matched population; and
3. Normal function, triangulated against data from different measurement techniques.

Beyond these contexts, impaired function may occur in a normal, adaptive system *when stressed*, for example by increases in volume or viscosity. This failure to adapt forms the basis of variants of the *volume-viscosity test* (Clavé et al. 2008) and other similar evaluations of oesophageal function e.g., provocative testing during swallowing.

4. Normal function but limited by failure to adapt to provocative testing.

The primary functions of oropharyngeal swallowing are to transport the swallowed material/bolus *both* safely and efficiently from the oral cavity into the oesophagus, while the function of oesophageal swallowing is to transport the bolus through the oesophagus into the stomach (Goyal & Mashimo 2006). Swallowing function is described in detail in Chapter 2.1, above.

While function refers to motor function and bolus transport function, the meaning of the term dysfunction may be less clear (Cook 1993, Allen 2016), incorporating both impaired and failed function.

In this thesis, three functional levels will be used throughout, *normal* meaning fully intact function, *impaired* meaning a degree of dysfunction between normal and complete failure, and *failed*, meaning complete failure as represented by airway penetration or a substantial failure of oesophageal bolus transport (Table 2.3).

Table 2.3 Swallowing Function Measurement

Swallowing Function	Normal	Impaired	Failed
Safe swallowing	Normal safe swallow	Penetration	Aspiration
Pharyngeal bolus transport	Normal transit	Increased above normative (95thP) for young healthy*	>50% bolus retention >0.1 on NRRS
Upper oesophageal sphincter	Relaxation Opening	Reduced opening below normative (5th P) for young healthy	Non-relaxation and biomechanical consequences Reduced opening (to be established)
Proximal oesophagus	Normal transit	Bolus transit lasting > 5sec*	Bolus retention
Distal oesophagus	Normal transit	Bolus escape	<80% liquid bolus; <70% increased consistencies clearance
Lower oesophageal sphincter	Barrier function Swallow-induced Relaxation	Unknown for barrier function Reduced relaxation	Reduced below normative (5th P) for young healthy Failed relaxation

Where other formal pre-existing definitions distinguishing normal function from impairment exist in the literature, such definitions will be used. For example, impedance based oesophageal liquid bolus clearance is defined as a drop to 50% of baseline and return to baseline prior to passage of the peak contraction at each impedance segment (Tutuian & Castell 2004), and clearance at all oesophageal segments in 80% of swallows, while oesophageal bolus clearance of increased consistencies is defined by a 70% success rate (Tutuian & Castell 2003, Nguyen et al. 2005, Bulsiewicz et al. 2009). Similarly, Rosenbek's

scale for penetration and aspiration (Rosenbek et al. 1996) is well establish and contains all the essential components needed to clearly define normal, penetration (impairment) and aspiration (failure). A key purpose of this research program was to establish normative ranges for HRM-I metrics in relation to functional impairments across the age range.

2.2.1 Normal function, as measured against a young, healthy population

It is, at this stage, unknown at what age, if any, a major decline in swallowing function occurs. This fundamental question is complex to answer due to the multiplicity, complexity and interdependence of the swallowing system. Most data as relates to swallowing function in the literature are captured in a young, healthy population. The oldest individuals in series of normal range from 48-64 years of age only (Ghosh et al. 2006, Sweis et al. 2011, Nieibisch et al. 2013, Bogte et al. 2013, Kessing et al. 2014, Weijenborg et al. 2014, Gao et al. 2015) and most published normative values for high-resolution manometry therefore apply to this (younger) population. What is interesting is that most patient populations are usually older.

How swallowing changes and at what age is a topic for investigation in this thesis. At this stage, it would be reasonable to assume swallowing to be normal in individuals up to forty years of age with some physiological decline beyond that age.

2.2.2 Normal function, as measured against an age-matched population

When reporting swallow function variables, it is considered appropriate to compare against an age-matched, and where possible, gender-matched cohort. This is particularly important in contexts where age and gender may have a significant influence on the results and less so when there are minimal or no age or gender effects. The concept that functional impairment is inherent to aging is uncomfortable for some readers and it is important to guard against an

ageist approach (WHO 2016). Furthermore, as age increases, potentially so does variability (Molfenter & Steele 2011, Kern et al. 2017), further complicating age-matched measurement.

Whereas it remains important to make age- and gender-matched comparisons, a different approach would be to define normal, impaired and failed function using objective measurements and then comparing such measurements against simultaneous (meaning at the same time) or concurrent (meaning within the same timeframe but separate) measurements of a different kind. I would refer to this approach as triangulation.

2.2.3 Normal function triangulated against data from a different measurement technique

There exists, for each function, a gold standard measurement technique and ground truths. The gold standard can be defined as the *best available test with a standard and known result* and a thoroughly tested technology which has a reputation in the field as a reliable method (Cardoso 2014). Ground truths are dogmatic ideas or expert opinion that are widely accepted but can't necessarily be exactly measured (Cardoso 2014).

Measurements are inherently fraught with technical or human error. This is particularly pertinent to the use of radiology or endoscopy, often used in assessing swallowing function, where marked inter-observer errors have been demonstrated (Kuhlemeier et al. 1998, Stoeckli et al. 2003, Mayinger et al. 2006, da Silva et al. 2010, Hyun et al. 2013, Baijens et al. 2013, Neumann et al. 2020). An attempt will be made within this research program to use objective forms of analysis, which includes for many components the addition of computer-based analyses, proven to be reliable (Omari et al. 2016).

During radiology, the use of the Rosenbek scale to determine penetration and aspiration is ubiquitous and therefore, reliability of this scale is high (Rosenbek et al. 1996, Baijens et al. 2014). However, such reliability may not be consistent across all bolus consistencies (Baijens

et al. 2014). Most videofluoroscopic swallowing investigations still do not use consistent bolus volumes or consistencies, which are a critical determinant of oropharyngeal swallowing function. Other instruments using during radiology vary in reliability but image analytical methods (Pearson et al. 2013) may be the most reliable amongst these.

2.2.4 Function during provocative swallowing

Function may be intact when tested using standard, smaller bolus volumes, and failed at larger volumes, increased consistencies or with provocative manoeuvres meant to test specific aspects of swallowing function. The literature suggests liquid volumes up to 20ml can be safely and reliably swallowed in a single swallow by healthy individuals of all ages (Ertekin et al. 1996, Clavé et al. 2008, Rofes et al. 2014, Aydogdu et al 2015). For liquid bolus functional failure is represented by aspiration, but for increased consistencies, failure may occur through large volume bolus retention. It is currently unclear what the downstream effects of upstream functional impairment or failure are.

Recently, provocative testing of oesophageal function has become more widely used and better defined (Misselwitz et al. 2020). This takes two main forms: increases in bolus consistency, potentially with testing of a standardized solid meal (Ang et al. 2017), or provocative manoeuvres meant to test specific functions such as multiple, rapid swallowing or the rapid drink challenge (Ang et al. 2017). Criteria are different for solid, as compared to liquid boluses (Sweis et al. 2011, Sweis et al. 2014, Ang et al. 2017)

For oesophageal provocative testing, normative values are established. For multiple rapid swallowing, a distal contractile integral (in mmHg.s.cm) in excess of the average for 10 liquid swallows is regarded as intact contractile reserve function (Shaker et al. 2013). This relates to the ability of this value to predict successful post-surgical outcomes (Stoikes et al. 2012). Only MRS performance (does it breach the ratio of one or not) is reported in relation to dysphagia

symptoms, so it is not clear whether the numerical value, above or below the defined threshold for weakness for example, makes a difference in this outcome.

In addition to contractile reserve function, the MRS also tests for deglutitive inhibition (failure defined as pan-pressurization of 20mmHg for more than 3cm - Carlson et al. 2016, Marin et al. 2018), and also for lower oesophageal sphincter relaxation.

In summary, in the modern form of manometric assessment, provocative tests make up an important component, however, interpretation of the results is still in flux and no single reliable method has yet been determined. Despite this, the reported measurements are all intended to relate to different aspects of physiological function.

2.2.5 Conclusion on defining normality

High-resolution manometry with impedance can rightfully be regarded as the gold standard test of oesophageal motor function. Motility or even functional findings do not always line up with symptoms. Despite the intention of classifying motility disorders on the premise that symptoms such as dysphagia or non-cardiac chest pain relate to specific motor patterns, symptoms have proven unreliable in this regard (Lazarescu et al. 2010, Dalmazo et al. 2012, Bogte et al. 2014, Xiao et al. 2014). This fact is pertinent when considering the biomechanical changes (or lack thereof) related to sensory changes in ageing. The entirety of the swallowing system has complex interdependencies, and the intention of this research program is to explore this system in its complexity to better guide care decisions for improved personal outcomes. Defining normal is but a starting point in this journey.

2.2.6 Conscious and subconscious awareness of declining swallowing function (sensory function)

While some older individuals are aware of an impaired ability to eat normally, others deny or are not consciously aware of swallowing function decline. The fact that some older individuals are not consciously aware of a decline in their swallowing function impacts on the reliability of self-reports of dysphagia or swallowing dysfunction. Some of these older individuals have subconscious awareness of such dysfunction and *auto-adapt* their eating and/or drinking behaviours to maintain safe swallowing (Smithard 2016). Such adaptation may take on several forms, including subconscious multiple swallowing behaviour, self-learnt adaptive swallowing behaviours such as slowed eating, or intentional or subconscious avoidance of certain foods. This phenomenon has not been well described or studied in depth but has long been recognised in clinical practice. Slow eating or food avoidance is detected through objective questionnaires such as the Sydney Swallowing Questionnaire (SSQ), which has a specific question regarding the time taken to eat a meal, Dakkak score, which asks around specific foods (Dakkak & Bennett 1991) or 4QT, a recently proposed screening method, which asks specifically regarding food avoidance (Tsang et al. 2020). Other subconscious behaviours such as supragastric belching may also impact on swallowing symptoms.

While auto-adaptive swallowing behaviour is thus increasingly being recognised, the exact biomechanics underlying such auto-adaptive behaviours are not well understood or studied. The older individual or their carer may recognise that certain foods repeatedly lead to coughing or choking episodes and will then start avoiding such foods. Commonly reported foods that cause difficulties are larger solids including meat or pieces of fruit and *bitty* or *crumbly* foods. Dysphagia diets would commonly avoid, on an empirical basis, such foods. I hypothesize that an avoidance of or reported coughing/choking episodes related to large solids or crumbly foods, is a manifestation of upper (o)esophageal sphincter dysfunction (UOS), meaning the UOS does not adequately open to allow such foods, or alternatively, such foods are not able

to traverse the UOS into the distal oesophagus with proximal retention. The hypopharynx (Dua et al. 2014) and proximal oesophagus (Woodland et al. 2015) are relatively more sensitive with resulting greater conscious awareness of retained bolus (Rao et al. 2003, Cock et al. 2020).

If awareness is increased for food bolus retained in the hypopharynx and proximal oesophagus, two additional considerations are relevant for older individuals. With a general decline in sensory function, failing swallowing adaptive behaviours, for example the ability to modulate UOS opening to bolus of differing volume or consistency, may lead to apparent downstream dysfunction. There may also be a lesser conscious or even subconscious awareness of distal oesophageal or lower oesophageal sphincter dysfunction or bolus retention.

Sensory function is critical to Pharyngo-UOS adaptive swallowing to bolus volume and viscosity (Cock et al. 2016 no 2; Ferris et al. 2021) but remains understudied (Humbert et al. 2009). Smell, taste and sensory discrimination reduces (Braun et al. 2022). Yoshinaka et al (2016) included what they called an *old old* group (aged c 80 years of age) and found even further reduced taste thresholds compared to younger-old groups. Little is known about the influence of oesophageal sensation. It seems obvious that oesophageal sensation may relate to symptoms but a direct correlation of symptoms and effects on motors function has not been shown (Lazarescu et al. 2010, Dalmazo et al. 2012, Bogte et al. 2014, Xiao et al. 2014).

2.2.7 The process of ageing in the context of functional decline

Ageing occurs as accumulating metabolic damage within cells, tissues and organ systems within the human body (Rockwood & Mitnitski 2011, Catic 2018). Starting at peak function in young adulthood (20-40 years of age), functional decline occurs at different rates within different tissues (epithelial, connective, neural and muscle) and is usually recognized as

decline beyond some arbitrary numerical threshold related to specific organ function (e.g., renal function below a set level of creatinine clearance).

Reserve function within the digestive tract offers a degree of protection from age-related functional decline until later in life. However, the complex swallowing mechanism consists of multiple different tissue types manifesting age-related changes in different ways and at different rates. To add further complexity, different subtypes of neural tissues (e.g., different sensory and motor fibers) or muscle tissues (striated and smooth muscle) may manifest functional decline at different stages and rates (Rockwood & Mitnitski 2007, Rockwood & Mitnitski 2011, Catic 2018).

Reserve function in the swallowing system is currently not well defined. In the oropharynx, airway protection and transit efficiency are both important functions. In the oesophagus, bolus transit, sphincter barrier function and distal oesophageal clearance are important functions. Furthermore, for the purpose of this thesis, beyond defining the term itself, we also need to consider the biomechanical manifestations in measuring swallowing reserve function.

2.2.8 The relationship of dysphagia in ageing to other *geriatric syndromes*

A decrease in functional reserve, the ability to compensate for impairments in normal physiological functioning, is a natural occurrence with ageing (Bauer & Sieber 2008). This loss of functional reserve can be viewed from two perspectives namely 1. a stepwise increase/accumulation of biological deficits (Rockwood & Mitnitski 2007, Rockwood & Mitnitski 2011) or 2. simultaneous progressive decline in function (Fried et al. 2001). These two models of functional decline borrow heavily from the concept of *frailty*, recently linked to age-related dysphagia, malnutrition and sarcopenia (Smithard 2018, Baijens et al. 2016, Smithard et al. 2020, Tsang et al. 2020).

Fried described frailty as a *phenotype* characterized by loss of muscle strength and weakness, accompanied by comorbidities and with adverse personal consequences for the individual (Fried et al. 2001). Fried's definition consisted of three of the following (Fried et al. 2001):

1. Unintentional weight loss (10 lb ≈ 4.5kg)
2. Self-reported weakness
3. Measured weakness (grip strength)
4. Slow walking speed, and
5. Low physical activity

Fried et al. (Fried et al. 2001) defined older age as being older than 65 years of age and found a 7% community prevalence of frailty. Frailty was also associated with an increased risk of disability (Makizako et al. 2015) and death (Shamliyan et al. 2013). Comorbidities were regarded as etiological risk factors for frailty (Fried 2001), rather than being an inherent component.

An alternative definition of frailty, offered by Rockwood (Rockwood & Mitnitski 2011), defined frailty as an accumulation of deficits. This model would align with the hypothesis that abnormal age-related oesophageal motor function results from accumulated deficits related to intercurrent illness such as diabetes mellitus, neurodegenerative or cardiovascular diseases such as stroke (Tack and Vantrappen 2011).

Recent work by Smithard and colleagues highlights the association of frailty and sarcopenia with undernutrition and dysphagia (Smithard et al. 2020, Tsang 2020). It is worthy to note that while these factors were interrelated, only dysphagia was correlated with *all* other factors (undernutrition, sarcopenia *and* frailty). Dysphagia is both a cause and a consequence of undernutrition, sarcopenia and associated muscle weakness.

Biological deficits accumulate to a threshold, beyond which they cannot be compensated for (Chen & Nguyen 2014). In their study of 572 nursing home residents over 75 years-of-age, Hébert et al. (Hébert et al. 1999) described functional decline in 20.1%, death in a further 7.5% and improvement in functioning in only 4.7%. Their study is in keeping with the concept of progressive decline *and* a small capacity for recovery or improvement.

Swallowing is a complex; multicomponent system and several known biologic deficits contribute to a decline in swallow function. Central nervous system inputs are critical in the control of volitional swallowing and modulation of reflexive pharyngeal swallowing (Jean 2001). We did see that the study by Humbert et al. (Humbert et al. 2009) demonstrated increased activation of brain areas related to swallowing in older, as compared to younger individuals. We can thus assume that a degree of neuroplasticity as relates to swallowing function is retained even in older age.

Conversely, although peripheral nerve function shows a slow rate of decline, autonomic sensory deficits are a well-known consequence of ageing and thus modulatory inputs in swallowing function may decline over time. Effects of ageing on connective tissue components of the swallowing system also have known functional consequences, such as a decrease in upper and lower oesophageal sphincter compliance (Cook et al. 1992) and increase in oesophageal stiffness (Gregerson 2008). Furthermore, there is a demonstrable reduction in cholinergic neurons and thus excitatory muscle function in the ageing gastrointestinal tract (Johnson et al. 1998, Cowen et al. 2000, Phillips et al. 2003, Wade & Cohen 2004, Cammileri et al. 2008, Salles 2009). More recently, a decline in inhibitory nitrergic neurons have also been demonstrated (Kim et al. 2017).

I am proposing a model of swallowing decline that follows the paradigm of a more slow, steady decline, with intercurrent illnesses superimposed, leading to temporary or permanent

increased rates of further decline, depending on interventions. If interventions can be instituted early, decline can be halted early with retention of functional reserve (Figure 2.13).

While biological decline cannot be halted, functional decline can be slowed, e.g., through such interventions as resistive exercise (Bauer & Sieber 2008). Emerging evidence suggest interventional exercise programs may improve biomechanical swallowing outcomes (Balou et al. 2019) but it is not yet clear which interventions to apply in which context, as other studies showed little improvement in objective measurements of swallowing function (Oh 2022).

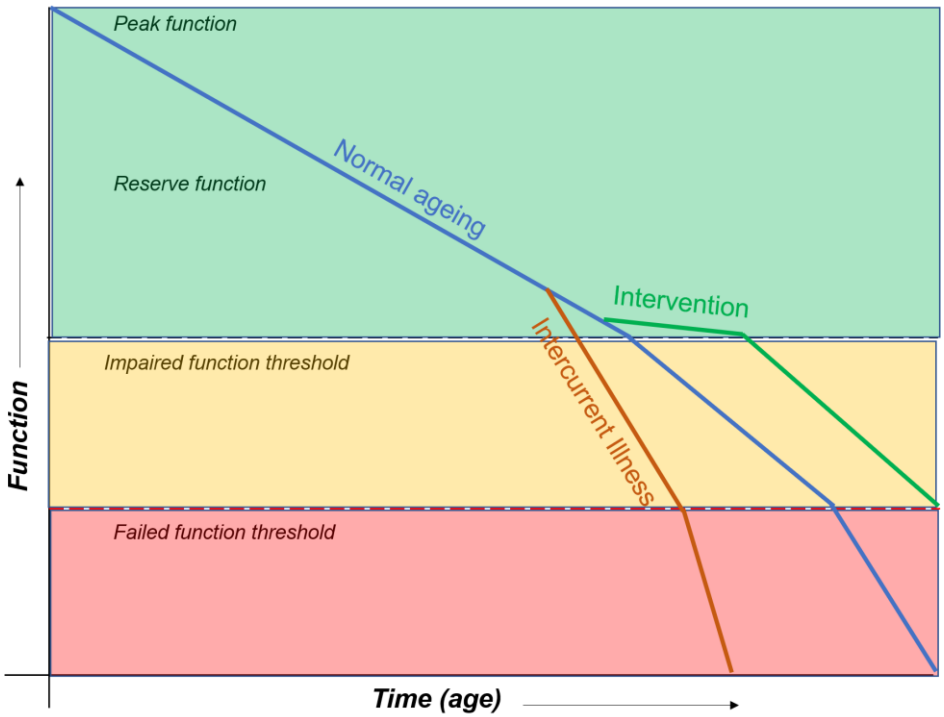

Figure 2.13 Functional decline (y-axis) over time (x-axis). During normal ageing function declines gradually (blue line) beyond a threshold indicating impairment toward a further threshold defining failure. Functional decline accelerates with intercurrent illnesses (red line) and amy improve with intervention (green line).

2.2.9 What is Known: Swallowing Changes in Community-Dwelling Older Persons

A recent systematic review of 15 studies reported an approximate prevalence of dysphagia of 15% in community dwelling older people (Madhavan et al. 2016). However, of note, multiple methodological difficulties were identified, including the use of unvalidated questionnaires and varying definitions of older, and only four studies were deemed of sufficient quality. Madhavan et al. (Madhavan et al. 2016) includes the often-quoted study by Bloem (Bloem et al. 1990) which asked a single question (do you have difficulty swallowing?) in 130 community dwelling adults over 87 years of age with a prevalence of 16%. This study demonstrates many of the issues identified in multiple studies in the review: an age range not meeting any common definition, three to four female participants for every male, a subjective response to a single unvalidated question and no corroboration or validation through independent or objective assessments.

Table 2.4 summarizes studies of dysphagia in older persons, published since the Madhavaram review and using validated instruments to assess swallowing function:

Table 2.4 Swallowing Impairment in Community Dwelling Older Persons (2015-2020)

	Subjective Measurements			**Objective Measurements**		
	Instrument	**Measuring**	**Abnormal n (%)**	**Instrument**	**Measuring**	**Abnormal n (%)**
Community Dwelling Older Persons						
Zhang 2020 (70-75 yrs; n=1017)	EAT 10	Dysphagia Screening	53 (**5**)	30ml WST		106 (**10**)
Zhang 2020 (>75 yrs; n = 1061)	EAT 10	Dysphagia Screening	78 (**7**)	30ml WST		229 (**22**)
Garand 2020 (> 60 yrs; n = 44)	EAT 10	Dysphagia Screening	5 (**11**)			
Nishida 2020 no 1 (>65 yrs; n = 3475)	Frailty Component	Frailty Assessment	431(**12**)			

Nishida 2020 no 2 (> 65 yrs; n = 220)	EAT 10	Dysphagia Screening	54 (**25**)	100ml WST	Swallowing Performance	Unknown
Igarashi 2019 (> 65 yrs; n = 510)	EAT 10	Dysphagia Screening	128 (**25**)			
Mulhuren 2018	DHI	Sw QOL	9 (**29**)	VFSS with MBSImp	Penetration/ Residue	4 (**12**)
Community-based needing care assistance						
Igarashi 2019 (> 65 yrs; n=886)	EAT 10	Dysphagia Screening	470 (**54**)			

The proportion of abnormality varied from 5 to 29% in independently living older persons. One study (Igarashi et al. 2019) also assessed dependent older persons living in the community and found a much higher prevalence of dysphagia (54%) in this cohort. In studies using both subjective (questionnaire) and objective (water swallow test – WST) measurements, objective testing identified abnormal swallowing performance in 2-3x the number of individuals reporting swallowing difficulties. However, in one study (Mulharen et al. 2018) objective assessment using video fluoroscopic swallowing studies (VFSS) identified *fewer* individuals compared to subjective reports. A recent analysis of general practice electronic health records in older persons in the United Kingdom found the dysphagia increased by age cohort above 65 years of age (Hollinghurst & Smithard 2022), occurring 23% more in those over 85 years of age (compared to 65-74 years of age).

Two further studies used subjective (SSQ: Nimmons et al. 2016) and objective (Volume-viscosity test: Serra-Prat 2012) means to study community dwelling older persons at time intervals. Nimmons et al. (Nimmons et al. 2016) found that between 2009 and 2012 older persons more often improved, rather than declines in subjective assessment. In contrast, Serra-Prat et al. (Serra-Prat et al. 2012) demonstrated an association of dysphagia in community dwelling older persons with future risk of not only malnutrition but also of

pneumonia. These studies demonstrate the value of objective over subjective assessment, in the context of variability and a decline in sensory awareness (Kern et al 2017) which may affect the result of subjective assessments.

Jiang et al (Jiang et al. 2016) undertook an analysis of the validity and reliability of swallowing screening tools used by nurses in different population groups. In summary, their study showed many current instruments lack robust assessment of reliability and validity.

In summary, no single, well validated screening instrument exists to assess swallowing function comprehensively and a wide range of rated of impairment are reported in community dwelling older persons (varying between 5 and 29%). Out of the current suite of available instruments, the conclusion thus is that an instrument needs to be selected according to the specific study question.

2.2.10 What is Known: Dysphagia in Older Persons in Nursing Homes

Reports of the incidence of dysphagia in older persons in nursing homes and hospitals varies greatly for more recent studies (Table 2.5), ranging from 9 to 67%. Reasons for this discrepancy are manifold and include the abovementioned differences between subjective and objective instruments, and further reliability issues.

Older studies demonstrate similar issues when using both subjective and objective assessment. Of particular interest is a study by Lin et al (Lin et al 2002) where subjects were asked whether they had dysphagia, and also assessed using objective timed water swallow test (Nathadwarawala 1990). More study subjects were tube fed than actually reported dysphagia (5.6%) while up to 51% met two objective criteria for dysphagia. Their results are similar to those in a study by Kayser-Jones (Kayser-Jones 1999) who demonstrated that

although dysphagia was only recognized as being a problem in 12% of residents in a nursing home, when bedside speech pathology assessments were performed, 55% of the residents were identified as having moderate to severe dysphagia. There are multiple other studies with similar findings (Nogueira & Reis 2013). These studies again speak to the marked challenges in the reliability of subjective reporting in older cohort.

Studies also reveal poorer health-related (Park 2013), quality of life (Tamura 2013), and mortality (Wirth et al. 2018, Hägglund et al. 2018) outcomes in dysphagic older nursing home residents. While mortality was increased in dysphagia, as compared to non-dysphagic nursing home residents, outcomes were much worse when associated with poor oral health (35 vs. 21.1% over 12 months)(Hägglund et al. 2019). Poor oral dental health in older persons is a predictor for bacterial chest infection (Langmore et al. 2002). In the largest study of aspiration pneumonia in more than 100 000 aged-care residents, age alone was not a highly significant risk factor, while the presence of artificial feeding, and by implication dysphagia, was (Langmore et al. 2002).

Table 2.5 Dysphagia in Nursing Homes (2013-2020)

	Subjective Measurements			**Objective Measurements**		
	Instrument	**Measuring**	**AbN (%)**	**Instr.**	**Measuring**	**AbN (%)**
Nursing Homes and Care Institutions						
Hägglund 2018 Diseased 12 months (≥ 65 yrs; n = 98)				TWST	Swallowing Performance	67%
Hägglund 2019 Survived 12 months (≥ 65 yrs; n = 293)				TWST	Swallowing Performance	51%

Streicher 2018 (≥ 65 yrs; n = 23549)	Single Question	Dysphagia Yes/No	13.4%			
Sarabia-Cobo 2016 (69-101 yrs; n = 2384)	EAT10	Dysphagia Screening	?	TWST	Swallowing Performance	70%
Van der Maarel-Wierink 2014 (≥ 65 yrs; n = 8119)	Single Question	Dysphagia Yes/No	9%			
Nogueira & Reis 2013 (unknown ave 82±10 yrs; n=266)	DST	Dysphagia Screening	40%	TWST	Swallowing Performance	38%
Park 2013 (65-74 yrs; n = 92)				GUSS	Screening Aspiration	43%
Park 2013 (≥ 75 yrs; n = 303)				GUSS	Screening Aspiration	55%

2.2.11 What is Known: Dysphagia in Hospitalised Older Patients

Although oropharyngeal dysphagia is recognized to occur in patients with stroke and other neurological conditions (Smithard 2016), it is often under recognized in the general older hospital population. Dysphagia is particularly prevalent older patients with malnutrition, frailty and sarcopenia (Smithard 2018). Dysphagia in acutely hospitalized older patients is associated with increased inpatient and subsequent mortality (Carrion et al. 2015), length of stay (LOS) and a decreased likelihood of returning to their own home (Carion et al. 2015, Cabre et al. 2010, Altman et al. 2011, Tsang et al. 2020). In addition, dysphagia has been associated with 40% greater health care utilization and expenditure, regardless of admission diagnosis, but in particular in stroke (Attrill et al. 2018). In this meta-analysis, length of stay (LOS) was numerically longer in the setting of dysphagia in all twenty-nine included studies.

Table 2.6 Dysphagia in Older Hospitalised Inpatients (selected studies 2015 to 2020)

	Subjective Measurements			Objective Measurements		
	Instrument	**Measuring**	**AbN (%)**	**Instr.**	**Measuring**	**AbN (%)**
Hospital Inpatients						
Tsang 2020 (75-102yrs; n =48) Frail Older	EAT10	Dysphagia Screening	45%			
Tsang 2020 (75-102yrs; n =48)	4 QT	OPD Screening	29%			
Spronk 2020 (59-80 yrs; n = 205) General Wards	EAT 10	Dysphagia Screening	23%	V-VST	Screening Aspiration Risk	17%
Peñalva-Arigita 2019 (>65 yrs; n=200)	EAT 10	Dysphagia Screening	42%	V-VST		29%
Umay 2019 (≥ 65 yrs; n = 1163)	EAT 10	Dysphagia Screening	Not reported			
Jørgensen2017 (unknown; n = 110)				V-VST	Screening Aspiration Risk	35%
Carion 2015 (≥65 yrs, n = 1662)				V-VST	Screening Aspiration Risk	47%
Carion 2015 ≥ 85 yrs				V-VST	Screening Aspiration Risk	86%

Varying methods are used to screen hospitalised older patients for dysphagia, when these are actually performed. Similarly, to previous descriptions in community dwelling and nursing home residents a greater proportion of dysphagia is detected using objective, as compared to subjective measures. For example, Lee et al. (Lee at al. 1999) found 28.2 vs 7.1% dysphagia in hospitalized older patients by objective, as compared to subjective assessment in the

geriatric inpatient setting (Lee 1999). When bedside testing is used, studies using different consistencies (as compared to a single consistency) perform better (Bours et al 2009).

Tsang et al (Tsang 2020) assessed twenty-nine instruments used to assess swallowing function to come up with the four questions most frequently included in existing questionnaires: 1. Do you cough/choke when eat and drink?; 2. Does it take you longer to eat your meals than it used to?; 3. Have you changed the type of food that you eat?; and 4. Does your voice change after eating or drinking? They used their results to devise the 4QT as a simple screening test. The 4QT has appeal in its simplicity and logic but not been compared to either objective or instrumental tests and more validation is needed.

Combined tools had also been developed screen for dysphagia by combining subjective and objective assessments in medical conditions known to be associated with dysphagia, such as neurological/head and neck conditions, geriatric syndromes, suspected aspiration pneumonias (Cichero et al. 2009). A combined screening tool may prove most successful in identifying and ultimately treating an at risk hospitalized population but is currently used in limited settings.

2.2.12 Conclusion (function and dysfunction in older persons)

In summary, impaired swallowing function and dysphagia is prevalent in community dwelling, institutionalized and hospitalized older persons. Impaired swallowing function appears to be particularly prevalent among the oldest old (Hollinghurst & Smithard 2022) and while oropharyngeal dysphagia is suspected (Cook 2009), the exact nature of this swallowing dysfunction in this age cohort is incompletely understood. Impaired swallowing function in older persons is demonstrably associated with an increased risk of malnutrition, pneumonia, disability and death. When assessing older persons for dysphagia, some form of validated

testing is better than no testing and, at face value, objective testing is likely to be more accurate than subjective testing, such as questionnnaires.

Using currently commonly available instruments or even instrumental assessments, swallowing impairment in older persons is incompletely understood. I am therefore proposing a robust biomechanical measurement of swallowing physiology and novel analyses of pressure and impedance data (as pressure-flow) in both healthy volunteers and patient cohorts.

The next section of this literature review will assess specifically current knowledge on manometry in ageing. This section has been published in the form of a literature review, which is included, in published form, in the appendices. Sections of this review, such as the discussion have been rewritten for the thesis. While the original intention was to focus on an older cohort (80 years and over), it became obvious early in the literature search that too few such studies existed related to manometry, prompting an expansion of the age range to include the (entire) population defined as older from 60 years of age onwards (WHO definition).

Chapter 2.3 Systematic Review of Manometry in the Assessment of Swallowing Impairment in Older Persons.

The published version (cf. article in Geriatrics in appendices) includes material which forms part of this thesis and removed from this version of the review, rewritten with a new discussion

2.3.1 Introduction

Impaired swallowing function and dysphagia are increasingly recognized when assessing community-dwelling, institutionalised, or hospitalised older persons (Altman et al. 2010, Sura et al. 2012, Clavé & Shaker 2015, Rommel & Hamdy 2016, Smithard 2016). We have seen how these factors impact on quantity and quality of life; malnutrition, dehydration, pulmonary aspiration and increased choking risk may follow (Altman et al. 2010, Sura et al. 2012, Serra-Prat et al. 2012, Clavé & Shaker 2015, Carrión et al. 2015, Rommel & Hamdy 2016, Smithard 2016, Carrión et al. 2017). A less well recognized factor impairing quality of life is the marked social isolation caused by the inability to eat a meal (Ekberg et al. 2002).

Sarcopenia and associated physical impairments and frailty may result in, or contribute to, dysphagia (Serra-Prat et al. 2012, Wakabayashi et al. 2014, Azzolino et al. 2019). Thus, a failure to recognise or adequately address swallowing disorders in older persons could trigger a downward spiral sarcopenia leading to dysphagia and worsening sarcopenia. This applies more so to hospitalized or institutionalized individuals (Cook 2009, Carrión et al. 2017, Bomze et al. 2021), however healthy, community- dwelling, older individuals are at risk (Serra-Prat et al. 2012). Measurement of swallowing impairment is challenging, and current methods, such as radiology, seem inconsistent in detecting age impairments in older persons. This review will focus on the use of pharyngeal and oesophageal manometry, with or without impedance, for the assessment of dysphagia symptoms in older persons.

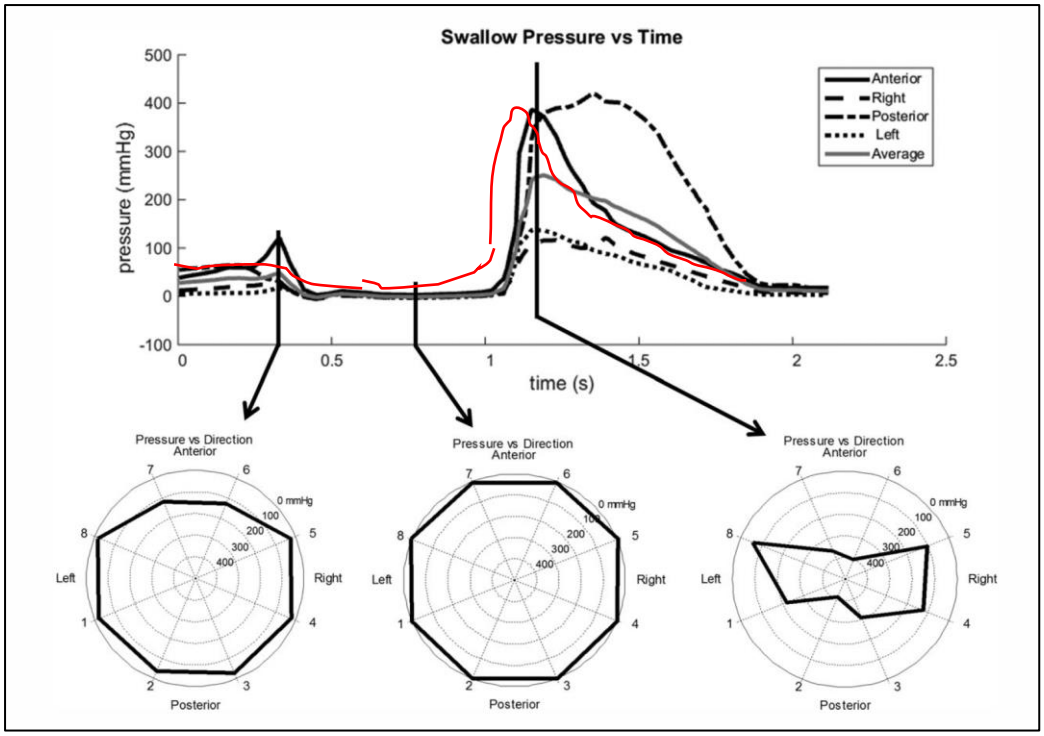

Figure 2.14

Three-dimensional structure of the upper oesophageal sphincter (UOS) (from Meyer 2016 – average shown as red line).

Manometry across the pharyngoesophageal segment must record the rapidly changing and widely varying pressures generated by asymmetrically contracting luminal structures (Figure 2.14) (Castell et al. 1990, Sears et al. 1991, Shaker & Lang 1994, Massey 2013, Meyer et al. 2016). Historically, it is widely regarded that traditional manometry equipment, using water perfusion, even with sleeve sensors, was unable to overcome these challenges (Shaker & Lang 1994). Therefore, solid-state transducers were developed that produce interpretable pharyngeal and UOS results (Shaker & Lang 1994, Massey 2013). The most recent iteration of this development employs sensor spacing of 1cm or less and is referred to as pharyngeal high-resolution manometry without (P-HRM) or with impedance (P-HRM-I) (Omari et al. 2019).

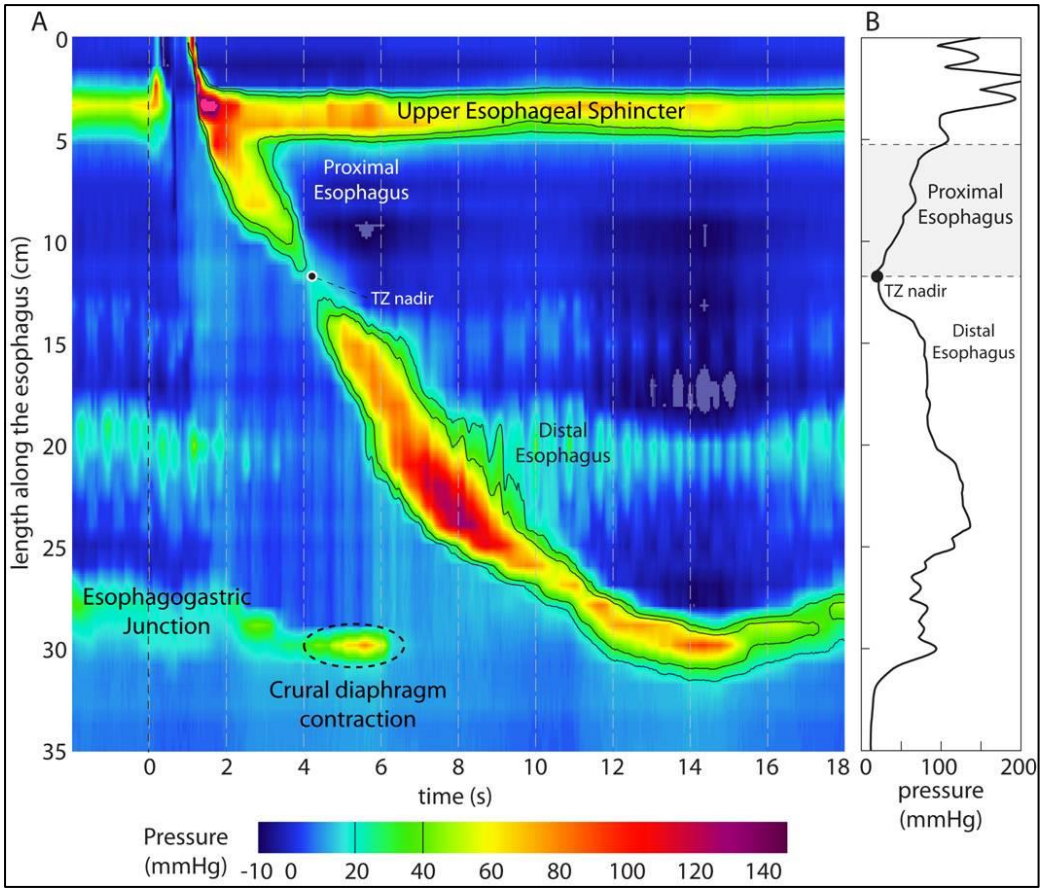

Figure 2.15

Oesophageal Pressure Topography

From https://en.wikipedia.org/wiki/High_resolution_manometry accessed on 30/06/2020

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Oesophageal manometry is used in conjunction with radiology and endoscopy to definitively diagnose major abnormalities of oesophageal peristalsis, such as achalasia (Pandolfino et al. 2008, Pandolfino et al. 2009, Bredenoord et al. 2012, Kahrilas et al. 2015, Kahrilas 2017, Yadlapati et al. 2021). Technologies have evolved from widely spaced water-perfused or solid-state pressure sensors used with a pull through technique to high-resolution manometry (HRM) (pressure sensors spaced at 1-2cm or less). The clinical use of HRM and oesophageal pressure topography – a contour map of oesophageal pressures - have markedly enhanced consistency, ease, and accuracy of major disorders of oesophageal peristalsis, and are now the standard of care in oesophageal motility disorders (Fox et al. 2004, Fox et al. 2008, Pandolfino et al. 2009, Bredenoord at al. 2012, Gyawali at al. 2013, Kahrilas at al. 2015, Yadlapati at al. 2021).

There is radiological evidence of reduced oesophageal bolus clearance in healthy older persons (Jou et al. 2012). Major oesophageal dysmotility, may be more common in older patients who present with oesophageal dysphagia, as compared to younger individuals with dysphagia and disease processes such as achalasia occur commonly in older patients in some studies (Ribeiro et al. 1998, Andrews et al. 2009). However, the data on oesophageal findings in older patients are inconsistent with some studies showing no difference between older and younger groups (Robson & Glick 2003, Andrews et al. 2008, Nakato et al. 2017, Shim et al. 2017). Manometry is often used to investigate dysphagia when bedside clinical assessments, radiology and endoscopic examinations fail to readily identify the cause of dysphagia or determine dysmotility. Manometry research has also enhanced our understanding of swallowing biomechanics and potential for intervention, including in the older population. For P-HRM, utilization of now widely available high fidelity solid-state technology is optimal, thus is the focus of this systematic review. The older population, with a higher prevalence of oropharyngeal dysphagia (Cook 2009) and potentially major disorders of peristalsis (Ribeiro et al. 1998, Andrews et al. 2009), is likely to benefit from improvements in technology offered by high-resolution studies.

2.3.2 Methods

The study design was based on the 2015 version of the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) (Shamsheer et al. 2015, Mohan et al. 2015). The focus of the investigation was on high-resolution manometry studies evaluating participants over 60 years of age (either healthy volunteer groups or dysphagia), with outcomes compared to young healthy controls (in healthy volunteer studies) or younger patients.

2.3.2.1 Eligibility criteria

Inclusion and exclusion criteria for studies are included as Table 2.7

Table 2.7 Manometry Review: Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Case control, Cohort, Observational.	RCT (drug trails, therapeutic interventions), Review, Cases, Case series.
At least one group ≥ 60 years of age.	Study focused on single disease process e.g., achalasia
Either healthy volunteers *or* a patient population with dysphagia included.	Surgery or radiotherapy involving the pharynx, UOS or oesophagus
Technical details of manometry procedure described.	Anorectal manometry
For pharyngeal studies the use of solid-state sensors, 3cm or less (*low-resolution*) or spaced at 1cm or less *high-resolution* (P-HRM).	For pharyngeal studies sensor spacing less than 3cm
For oesophageal studies both l*ow-resolution* (> 1cm sensor spacing) and *high-resolution* (<1cm or less), without or with impedance (HRM/HRMI).	Language other than English (LOTE) without available translation. (Simultaneous publication of English translation for LOTE articles)

2.3.2.2 Participants

Definitions of ageing vary. The definition used when referring to the older population was individuals aged *60 years of age and older*, in keeping with the *World Health Organization* formal definition of older age (WHO, 2015), however age 65 and older is mostly in keeping with a majority view of the terms *aged, older, elderly or geriatric*. Our original intention was to use 65 as a cut-off, however many important studies of age-related manometry changes used sixty as age cut-off. The comparator was human participants between 18 and 59 years of age. A wide variety of ages are defined or regarded as being *older*, with some defining patients as young as in their 40's or 50's as *older* (Dantas et al. 2010, Jung et al. 2015).

2.3.2.3 Interventions

Participants had to undergo manometry using standardized (commercially available) manometry equipment. Reports had to include details on the equipment used, technical details on sensor technology, sensor spacing and catheter configuration and in addition, participant posture, volume, consistency, and type of the boluses swallowed.

2.3.2.4 Comparators

Normative values had to be either standardized for the equipment configuration or reported based upon inclusion of a young participant comparator group.

2.3.2.5 Outcomes

When this study was conducted there was no universally accepted metrics for the assessment of pharyngeal or UOS function. Subsequently a consensus version of pharyngeal and upper oesophageal sphincter metrics has been published for P-HRM (Omari et al. 2020). For an interpretation of pharyngeal manometry related to functional outcomes such as pulmonary aspiration risk and pharyngeal residue also see Chapter 4 (cf. Cock & Omari 2017)

The UOS is tonically contracted and needs to neurogenically deactivate to relax and open. **UOS resting or basal pressures** give an indication of this basal tone. Another important aspect measured during pharyngeal manometry relates to opening of the UOS, or cricopharyngeal/UOS dysfunction (Cook 2006, Allen 2016) whereby UOS opening is inadequate for the size/volume of the bolus swallowed due a non-opening and/or non-relaxing UOS high pressure zone. UOS dysfunctions commonly result from neurogenic or myogenic causes affecting **UOS relaxation** and **UOS opening extent** (Cook et al. 1989). Restricted opening commonly leads to increased **intrabolus pressure** above and pressure gradient across the sphincter, provided pharyngeal contractility is sufficiently propulsive (Williams et al. 2001, Pal et al. 2003). Pharyngeal contractility is commonly reported as a peak pressure (**PeakP**) per sensor or average across a region. Some studies also reported the **duration** of the pharyngeal swallow. Combining both pressure and duration with length, pressure contractile integrals are also described per region, with a global pharyngeal contractile integral (**PhCI**) (Nativ-Zeltzer et al. 2016, O' Rourke et al. 2017, Omari et al. 2019).

Reported outcomes for Pharyngeal studies are included below (Table 2.8):

Table 2.8

Pharyngeal Measurements
1. Upper oesophageal sphincter basal pressure (UOS-BP in mmHg).
2. Upper oesophageal sphincter relaxation a. Duration (UOS-RT) b. Integrated relaxation pressure in 0.25 seconds (UOS-IRP in mmHg)
3. UOS opening extent on radiology or impedance base (UOS Max Adm in milliSievert – mS – see later)
4. Intrabolus pressure above sphincter (IBP in mmHg at 1cm above UOS).
5. Pharyngeal contractility – (PeakP or PhCI) and duration (milliseconds - ms)

With few exceptions the most recent iteration of the Chicago Classification of distal oesophageal motility available at the time – version 3.0 (Kahrilas et al. 2015) - was used. **Oesophagogastric junction (OGJ) barrier function** including lower (o)esophageal sphincter (**LOS**) resting pressure and **relaxation** forms a critical component of the manometric assessment of oesophageal function. Following on from this, **distal oesophageal contractility** leads to the completion of bolus flow through the OGJ. Few studies specifically report on **proximal oesophageal contractility** in older subjects (Dantas et al. 2010, Nativ Zeltzer et al. 2016) – no comprehensive assessment of this aspect was possible, and more studies are needed. A few studies reported on oesophageal peristaltic success, expressed as a proportion (%) successful peristalsis. Table 2.9 includes the outcomes reported for oesophageal studies.

Table 2.9

Oesophageal Measurements
1. Oesophagogastric junction barrier function (LOS resting pressure in mmHg, OGJ contractile integral in mmHg.cm).
2. Lower oesophageal sphincter relaxation pressure (integrated relaxation pressure in 4 seconds IRP4 in mmHg).
3. Contractility of the proximal oesophagus (limited data) (proximal contractile integral/PCI – pressure x length x duration in mmHg.cm.s).
4. Contractility of the distal oesophagus (as mean peak pressure in mmHg or distal contractile integral – pressure x length x duration in mmHg.cm.s).
5. Oesophageal peristaltic success (% successful peristalsis).

2.3.2.6 *Settings*

There were no restrictions on the setting.

2.3.2.7 *Language*

English language articles were included. Articles in other languages were only included if a full translation in English was simultaneously published.

2.3.2.8 Information sources

The literature search strategy was developed using medical subjects headings (MeSH) terms related to manometry in older subjects. Medline (OVID interface, 1948 onwards), Pubmed at https://www.ncbi.nlm.nih.gov/pubmed and Web of Science core collection v5.29.

2.3.2.9 Search Strategy

A search was undertaken for English language articles dated 1948 to 2018 using the search terms manometry AND age/aging/elderly/older AND *either* pharynx/pharyngeal plus high-resolution or oesophagus/oesophageal. Studies of anorectal manometry were excluded.

Cross referencing and the author's own collections were used to supplement the search strategy.

2.3.2.10 Study Records

2.3.2.10.1 Data management and Selection Process

Records of all searches (titles only) were saved in a folder on a password protected and fire walled personal computer. Eligible articles were saved in .pdf format in a shared folder and where needed printed out for reading. Titles, abstracts and, where necessary, article text was scanned to assess eligibility for inclusion if the study contained data on a participant group as defined (see Table 1). Searches were undertaken by author CC and screened for inclusion by author CC and supervisor TO independently.

2.3.2.10.2 Data collection process

Data reporting was specific for methodology during manometry. Differences in equipment (e.g., catheter specifications/diameter (Ferris et al. 2018) may account for different values for the same variable. Interpretation of data should be undertaken with this knowledge and as such, rather than performing a meta-analysis, functional interpretation was applied to the data (Table 2.11).

2.3.2.10.3 Data, Outcomes and Prioritization

Consideration was given to the functional and clinical relevance of findings. Pharyngeal and oesophageal studies were grouped into those in healthy volunteers, or symptomatic patients.

2.3.2.10.4 Risk of bias

Bias was assessed as per table 8.5 in the Cochrane Handbook for Systematic Reviews of Interventions at ***http://handbook-5-1.cochrane.org/*** **.** Possible bias was assessed for each of the six domains described: selection, performance, detection, attrition, reporting and other sources of bias.

Results for biases are included in the results section below.

2.3.2.10.5 Data Synthesis

Due to heterogeneity in measurement techniques and the potential for catheter configuration or measurement technique to influence results, methodology was focused on regional changes related to functional swallowing outcomes.

Studies in patients (but not healthy volunteers) were rated for **quality** (very high to low from A-D) and **strength of recommendation** *(strong or weak for or against)* with the overriding question on whether the study results/outcomes were likely to change clinical management. An adaptation of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) scale for diagnostic tests , specifically adapted for oesophageal manometry was applied (Table 2.10)(Guyatt 2008, Schünemann 2008). Study quality was modified as described within GRADE (Guyatt 2008, Schünemann 2008).

Table 2.10 Grading of Recommendations Assessment Development and Evaluation (GRADE) applied to Manometry Studies

Quality of Evidence	Strength of recommendation
High quality (A) e.g. High Resolution Manometry	Strong recommendation for (1)/↑↑
Moderate Quality (B)	Weak recommendation for (2)/ ↑
Low Quality (C) e.g. Low Resolution Manometry	Weak recommendation against (2)/↓
Very low quality (D)	Strong recommendation against (1)/↓ ↓

2.3.3 Results

2.3.3.1 Literature Search and Study Characteristics

The results of the literature search for pharyngeal manometry (Figure 2.16) and oesophageal manometry (Figure 2.17) are reported (see over). Two hundred and fifteen studies of pharyngeal manometry and nine hundred and twenty-seven studies of oesophageal manometry were retrieved. During the Web of Science search, alternate possibilities such as “anorectal” were specifically excluded. Terms such as “aging” or “older” produced more focused results, as compared to broad search terms such as “age”.

2.3.3.2 Manometry Studies

The results of the manometry studies are summarized (Table 2.11), with measurements in the subsequent table (Table 2.12). These tables have been altered to remove studies otherwise included in this thesis – the original study can be compared (appendix) of pharyngeal manometry and nine hundred and twenty-seven studies of oesophageal manometry were retrieved.

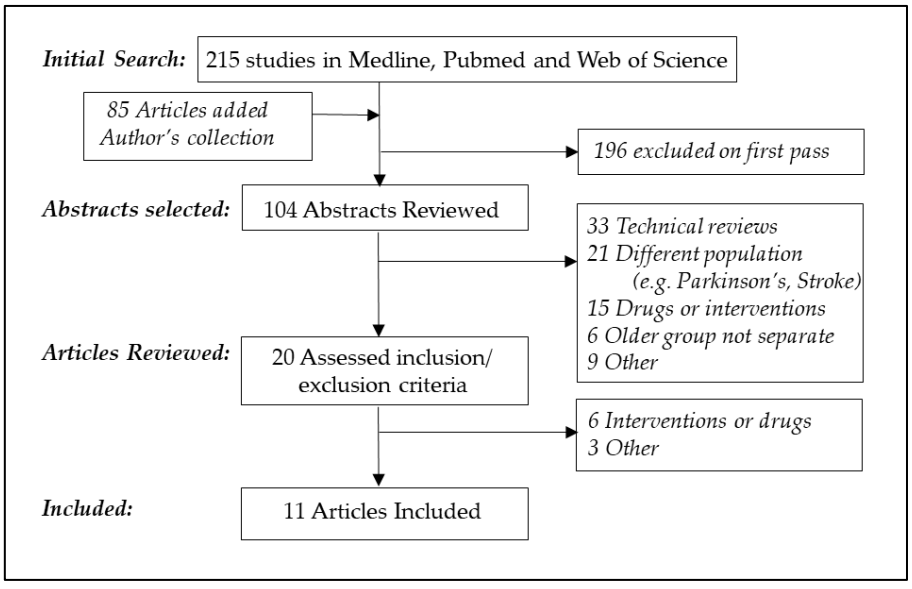


Figure 2.16 Search Strategy for Pharyngeal Manometry in Older Persons

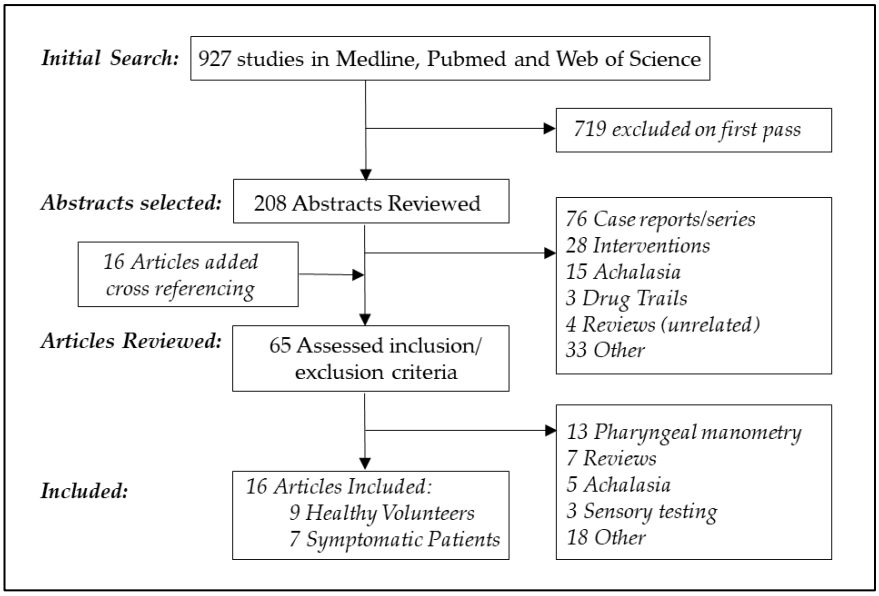


Figure 2.17 Search Strategy for Oesophageal Manometry in Older Persons

Table 2.11 **Studies of Pharyngeal and Oesophageal Manometry in Older Persons**

Study	Population	Methods	Main findings in Older
Pharyngeal Manometry			
Shaker R, *et al.* Effect of aging and bolus variables on pharyngeal and upper esophageal sphincter motor function. Am J Physiol 1993; 264:G427-G432.	Older (aged 76±1.5 yrs) n = 12 Younger (aged 25±1 yrs) n = 14 Healthy Volunteers	Videomanometry Gaeltec MMI spaced 1.5cm	Resting UOS pressure lower Hypopharyngeal peak pressures increased Duration of hypopharyngeal pressure increased
Dejaeger E *et al.* Manofluorographic Analysis of Swallwing in the Elderly. Dysphagia 1994; 9:156-161	Older (aged 80±5 yrs) n = 16 Younger (aged 28±8 yrs) n = 20 Healthy Volunteers	Video manometry Tranducers at 4cm, 1.5cm intervals	Incomplete UOS relaxation in 18% in older group Less negative pressure at UOS in older
McKee GJ, *et al.* Does age and sex affect pharyngeal swallowing? *Clin Otolaryngol* 1998; 23:100-106.	Older (60-85 yrs) n = 37 Younger (21-40 yrs) n = 36 Healthy Volunteers	Manometry 2cm spacing Konigsberg	UOS resting pressure decreased UOS opening earlier when referenced to UOS closure (i.e. longer duration of UOS relaxation) Less generation of negative pressure at the UOS in older
Kern M, *et al.* Comparison of Upper Esophegeal Sphincter Opening in Healthy Asymptomatic Young and Elderly Volunteers. *Ann Otol Rhinol Laryngol* 1999; 108:982-989.	Older (75±2.8 yrs) n = 14 Younger (32±2.7 yrs) n = 14 Healthy Volunteers	Videomanometry Gaeltec MMI spaced 1.5cm 5 & 10ml liquid barium boluses	Duration of UOS opening longer Duration of UOS maximally relaxed longer Significantly higher IBP above UOS (5&10ml L) UOS opening decreased (in AP diameter for 5ml)
*Meier-Ewert HK *et al.* Effect of Age on Differences in Upper Esophageal Sphincter and Pharynx Pressures Between Patients With Dysphagia and Control Subjects. *Am J Gastroenterol* 2002; 96:35-40.	*Healthy Volunteers:* Older (61-91 yrs) n = 15 Younger (32-59 yrs) n = 18 *Patients:*	Manometry Konigsberg 1.5cm, 2cm s	Decreased UOS resting pressure lower (significant in controls) Increased UOS residual pressure during solid bolus swallows only in healthy volunteers

	Older (60-88 yrs) n= 26 Younger (32-58 yrs) n = 15		Decreased pharyngeal peak pressure during solid bolus swallows only in patients
Van Herwaarden MA, *et al.* Are Manometric Parameters of the Upper Esophageal Sphincter and Pharynx Affected by Age and Gender? *Dysphagia* 2003; 18:211-217.	Older (>60 yrs) n = 23 Younger (<60 yrs) n = 61 Healthy Volunteers	Manometry Konigsberg 1.5cm, 2cm s	Decreasing UOS resting pressure correlated with age (r = -0.41; P < 0.001) and lower UOS residual pressure higher (liquids & solids) UOS-RT shorter (liquids, solids); UOS relaxation rate lower for all consistencies Pharyngeal amplitude increased Duration of contraction longer
Bardan E, *et al.* Effect of aging on bolus kinematics during the pharyngeal phase of swallowing. *Am J Physiol* 2006; 290: G458-G465.	Older (70-85 yrs) n = 8 Younger (18-40 yrs) n = 8	Videomanometry Study focused on bolus kinematics.	Bolus head (but *not* the bolus tail) slows significantly in the region between the epiglottis and UOS o*nly* in older Negative pressure at the UOS occurred less often: 41 vs 53% for liquids (n.s.) and 55 vs 83% of solids (P = 0.02)
Nativ-Zetzer *et al.* Pressure topography metrics for high-resolution pharyngeal-esophageal manofluorography – a normative study of younger and older adults. *Neurogastroenterol Motil* 2016; 28(5):721-731.	Older (aged 60-80 yrs) n = 22 Younger (aged 21-40 yrs) n = 22	High-resolution manometry Manoscan 4.2 & 2.75mm diameter catheters	Contractile integrals: PhCI, VPCI, TBI, and HPCI significantly greater (p<0.05) Integrated UOS relaxation pressure (UOS-IRP) greater (p<0.05) for all bolus trials. Proximal esophageal contraction (PCI) reduced
Yoon *et al.* Videofluoroscopic and Manometric Evaluation of Pharyngeal and Upper Esophageal Sphincter Function During Swallowing *J Neurogastroenterol Motil*, Vol. 20 No. 3 July, 2014	26 asymptomatic volunteers (12 men and 14 women; age, 19-81 years). Correlation with age reported.	High-resolution manometry Given Imaging	A significant correlation was shown between Decreasing hypopharyngeal CI vs age Decreasing median intrabolus pressure at UOS vs. age Decreasing nadir pressure at UOS vs. Age

Esophageal Manometry			
Healthy Volunteers			
Besanko *et al.* Changes in Esophageal and Lower Esophageal Sphincter Motility with Healthy Aging	Older (≥65 years) n = 10 Younger (<40 years) n = 10	Low-resolution Water perfused Dentsleeve; Trace!	Reduced lower esophageal relaxation in older group in supine, as well as upright posture and with increased bolus consistencies. Trend towards lower LOS resting pressure
Dantas *et al.* Effect of Age on Proximal Esophageal Response to Swallowing. *Arq Gastroenterol* 2010 Oct-Dec; 47(4)339-343.	Group I (18-30 yrs) n = 20 Group II (31-50 yrs) n = 27 Group III (51-74yrs) n = 22 Group C (III aged 51-59 yrs) n = 14 Group D (III aged ≥ 60 yrs) n = 8	Low-resolution Medizintechnik Polygram Upper GI	No difference in amplitude. Duration longer in youngest group Trend towards lower amplitude in group aged over 60 years of age (not statistically significant)
Grande *et al*. Deterioration of Esophageal Motility With Age: A Manometric Study of 79 Healthy Subjects. *Am J Gastroenterol* 1999; 94(7): 1795-1801	Six age cohorts (total n = 79) Sixth age cohort aged ≥ 65 yrs n = 13	Low-resolution Arndorfer, Beckman instruments	LOS resting pressure reduced LOS overall length increased UOS pressure and length reduced Maximum peristaltic wave amplitude reduced in the distal (but not significantly proximal) oesophagus Simultaneous contractions occurred more commonly in older subjects
Ferriolli *et al.* Aging, Esophageal Motility, and Gastroesophageal Reflux. *J Am Geriatric Soc* 1998; 46:1534-1537	Group I (20-30 yrs) n = 20 Group II (50-60 yrs) n = 10 Group III (70-80 yrs) n = 10 Healthy volunteers	Low-resolution Narco Bio 5ml liquid and viscous boluses supine	LOS resting pressure similar Contractile metrics similar Increased frequency of impaired peristalsis Clearance of scintigraphic reflux decreased

Nishimura *et al.* Effect of Aging on the Esophageal Motor Functions. *J Smooth Muscle Res* 1996; 32:43-50.	Group 1 (<50 years) n = 11 Group 2 (50-59 yrs) n = 15 Group 3 (60-69 yrs) n = 11 Group 4 (≥ 70 yrs) n = 10	Low-resolution Arndorfer 3-5ml liquids, supine	Trend towards lower LOS resting pressure No difference in nadir LOS pressure (relaxation) Lower proportion successful peristalsis ≥ 70 yrs Contractile amplitude reduced in ≥ 70 yrs
Richter *et al.* Esophageal Manometry in 95 Healthy Adult Volunteers. *Dig Dis Sci* 1987; 32:583-592.	95 Healthy volunteers Older group (≥ 60 yrs) n = 13	Low-resolution Arndorfer Beckman instruments 5ml liquids, supine	No difference in LOS resting pressure Contractile amplitudes similar Duration contraction longer
Khan *et al.* Esophageal Motility in the Elderly. *Dig Dis* 1977; 22(12):1049-1054.	Older group (≥ 60 yrs) n = 49 Young group (< 40 yrs) n = 43 Asymptomatic per questionnaires	Low-resolution Water perfused 5ml liquids	No difference in LOS resting pressure LOS relaxation reduced (82.2% vs. 94.1%; P < 0.003) Reduced amplitude distal and upper oesophagus Increased disordered contractions (25.3 vs 8.2%; P < 0.001)
Nakato *et al.* Age-Related Differences in Clinical Characteristics and Esophageal Motility in Patients with Dysphagia. *Dysphagia* 2017; 32:374-382.	Group A (≥ 65 years) n = 47 Group B (45-65 yrs) n = 42 Group C (< 45 yrs) n = 27 Dysphagia symptoms	High-resolution impedance manometry (HRIM) Sandhill	Overall average Chicago classification metrics were similar Major motility disorders occurred in 28% of older and 39% of younger dysphagia cases. No difference in diagnoses between groups.

Dysphagia Patients			
Nakato *et al.* Age-Related Differences in Clinical Characteristics and Esophageal Motility in Patients with Dysphagia. *Dysphagia* 2017; 32:374-382.	Group A (≥ 65 years) n = 47 Group B (45-65 yrs) n = 42 Group C (< 45 yrs) n = 27 Dysphagia symptoms	High-resolution impedance manometry (HRIM) Sandhill	Overall average Chicago classification metrics were similar Major motility disorders occurred in 28% of older and 39% of younger dysphagia cases. No difference in diagnoses between groups.
Shim *et al.* Effects of Age on Esophageal Motility: Use of High-resolution Esophageal Impedance Manometry. *J Neurogastroenterol Motil* 2017; 23:229-236.	Group A (≥ 65 years) n = 62 Group B (40-65 yrs) n = 185 Group C (< 40 yrs) n = 32 All symptoms	High-resolution impedance manometry (HRIM) Sandhill	Overall average Chicago classification metrics were similar Upper oesophageal sphincter resting pressures measured and reported to be lower in older (Group A 63.8mmHg±32.2 vs. Group B 92.5±49mmHg and Group C 92.7±46.0mmHg; P < 0.001)
Besanko *et al.* Lower esophageal sphincter relaxation is impaired in older patients with dysphagia *World J Gastroenterol* 2011; 17(10):1326-1331.	Older group (≥ 80 yrs) n = 19 Young group (< 50 yrs) n = 19 Dysphagia symptoms Achalasia excluded	Low-resolution Water perfused Dentsleeve; Trace! 5ml liquids, solids Left lateral, upright	Resting LOS pressure higher (23.4±3.8 vs 14.9±1.2 mmHg; P < 0.05) Nadir LOS pressure higher 2.3±0.6 vs. 0.7±0.6mmHg; P < 0.05) Restitution of LOS earlier Amplitude and duration of contractions similar
Andrews *et al*. Age and gender affect likely manometric diagnosis: Audit of a tertiary referral hospital clinical esophageal manometry service. *J Gastroenterol Hepatol* 2009; 24:125-128.	Older group (≥ 65 yrs) n = 135 Young (n = 317): Group 1 (17-24 yrs) n = 14 Group 2 (25-44 yrs) n = 87 Group 3 (45-59 yrs) n = 216	Low-resolution Water perfused Dentsleeve; Trace! 5ml liquids, solids	Increased abnormal studies (79% vs. 57%; P=0.013) Trend towards increased spastic type motility (P = 0.06)

	All symptoms	Left lateral, upright	
Andrews *et al.* Is esophageal dysphagia in the extreme elderly (≥ 80 years) different to dysphagia in younger adults? A clinical manometry service audit. *Dis Esophagus* 2008; 21:656-659.	Older group (≥ 80 yrs) n = 23 Young group (< 50 yrs) n = 23 Dysphagia symptoms	Low-resolution Water perfused Dentsleeve; Trace! 5ml liquids, solids Left lateral, upright	Resting LOS pressure higher (26.1±3.7 vs 16.8±1.9 mmHg; P = 0.03) Increased failed peristalsis (63 vs 32%; P = 0.006) Manometric diagnoses similar Fewer with heartburn symptom in addition
Robson & Glick. Dysphagia and Advancing Age. Are Manometric Abnormalities More Common in Older Patients? *Dig Dis Sci 2003*; 48(9): 1709-1712.	Older group (≥ 65 yrs) n = 53 Young group (18-45 yrs) n = 53 Dysphagia symptoms	Low-resolution Water perfused Medtronic 5ml liquids, supine	Equal number of abnormal studies (82% vs. 77%; P =NS) and achalasia diagnoses (32% vs. 34%; P = NS) LOS resting pressure, relaxation and oesophageal contractility similar. Peristaltic failure in 53% older and 40% young (P = NS)
Ribeiro *et al.* Esophageal Manometry: A Comparison of Findings in Younger and Older Patients. *Am J Gastroenterol* 1998; 93:706-710.	Older Group (≥ 75 yrs) n = 66 Young (≤ 50 yrs) n = 122 All symptoms	Low-resolution Solid state Konigsberg 5ml liquids	Dysphagia more common reason for referral LOS resting pressure similar (28.6mmHg vs. 27.2mmHg). LOS length similar. Peristaltic failure in 37% vs 22% (P < 0.005) Amplitude of contractions similar More simultaneous contractions (15 vs 4%; P < 0.02) Lower UOS resting pressure (49.6 vs 77.4mmHg; P < 0.002) and less negative residual pressure Older patients more likely to have achalasia (15.2 vs. 4.1%; P < 0.05) or spastic disorders (16.6 vs. 5%; P < 0.05)

Table 2.12 Summary of Metrics for Manometry in Older Persons.

Average values with SEM (ave±sem) or median values with 25th and 75th percentiles: (med [25th; 75th])

Study	Metric	Older	Younger	P-value	Interpretation (older group relative to younger group)
Upper Oesophageal Sphincter Function					
UOS Resting Pressure					
Shaker et al. 1993	UOS-RP (mmHg)	43±5	71±8	<0.01	Lower UOS resting pressure
Mc Kee et al. 1997	UOS-RP (mmHg)	44	70	<0.001	Lower UOS resting pressure
Meier-Ewert et al. 2001 (healthy volunteers)	UOS-RP (mmHg)	52±6	86±9	<0.05	Lower UOS resting pressure
Van Herwaarden et al. 2003	UOS-RP (mmHg)	46[20;116]	78[34;164]	<0.001	Lower UOS resting pressure
Meier-Ewert et al. 2001 (patients)	UOS-RP (mmHg)	65±9	96±15	n.s.	Similar UOS resting pressure
Intrabolus Pressure above UOS (5ml Liquids)					
Kern et al. 1999	Hypopharyngeal IBP	14±2	7±1	< 0.05	Higher
UOS Relaxation pressures (5ml Liquids)					
Meier-Ewert et al. 2001 (healthy volunteers)	UOS residual pressure (mmHg)	5.1±1.2	7.4±2.7	n.s.	Similar residual pressure
Meier-Ewert et al. 2001 (patients)	UOS residual pressure (mmHg)	3.5±1.5	-0.4±3.5	n.s.	Similar residual pressure
Van Herwaarden et al. 2003	UOS residual pressure (mmHg)	2.5(-8.4-14.5)	-3(-9.6-12)	<0.01	Higher residual pressure Decreased extent UOS relaxation
Nativ-Zeltzer *et al.* 2016	UOS-IRP (mmHg)	4±6	-3±4	<0.05	Decreased extent UOS relaxation
Duration of UOS relaxation/opening (5ml Liquids)					
Kern et al. 1999	Total duration UOS opening Maximum opening	612±9 ms 166±14 ms (27%)	571±8 ms 128±12 ms (22%)	< 0.05 < 0.05	Increased duration UOS relaxation
Meier-Ewert et al. 2001 (healthy volunteers)	UOS-RT (ms)	554±47	605±38	n.s.	Similar relaxation time
Meier-Ewert et al. 2001 (patients)	UOS-RT (ms)	525±35	470±39	<0.05	Increased duration UOS relaxation
Van Herwaarden et al. 2003	UOS relaxation time (50% drop and return to 50% baseline)	221 (75-379)	260 (133-535)	< 0.05	Decreased duration below 50% of baseline
UOS Opening Extent (5ml Liquids)					

Shaw et al. 1995	Lateral projection/sagittal diameter (mm) AP projection/transverse diameter (mm)	9.3±0.5 15±0.8	9.2±0.1 19.2±0.8	n.s. < 0.001	Decreased lateral opening extent
Kern et al. 1999	Lateral projection/AP diameter (mm) AP projection/Lateral diameter (mm)	11±0.4 21±4	12.6±0.6 20±5	< 0.05 n.s.	Decreased AP opening extent
UOS post-swallow Contractility (5ml Liquids)					
Nativ-Zeltzer *et al.* 2016	UOS-CI (mmHg.cm.s) UOS-PeakP (mmHg)	405±170 214±72	408±170 205±46	n.s. n.s.	Similar post-swallow UOS contractility
Pharyngeal Contractility (5ml Liquids)					
Shaker et al. 1993	Hypopharyngeal PeakP (mmHg) Duration hypopharynx (ms)	196±12 437±69	137±9 204±21	< 0.01 <0.01	Increased hypopharyngeal contractile vigor and duration
Meier-Ewert et al. 2001 (healthy volunteers)	Pharyngeal PeakP (mmHg) Duration pharyngeal contraction (ms)	182±20 763±64	139±13 593±55	n.s. n.s.	Similar pharyngeal contractility
Meier-Ewert et al. 2001 (patients)	Pharyngeal PeakP (mmHg) Duration pharyngeal contraction (ms)	96±15 712±64	144±21 712±58	< 0.05 n.s.	Decreased contractile vigor in patients
Van Herwaarden et al. 2003	Pharyngeal PeakP (mmHg) Duration pharyngeal contraction (ms)	152(44-379) 448(324-835)	133(53-220) 396(187-628)	<0.05 <0.05	Increased pharyngeal contractile vigor and duration
Nativ-Zeltzer et al. 2015	P-max (PeakP) (mmHg) PhCI (mmHg.cm.s)	249±54 363±110	211±64 256±84	<0.05 <0.05	Increased pharyngeal contractility
Oesophageal Studies:					
Esophagogastric junction (OGJ) barrier function					
Healthy Volunteers					
Besanko *et al.* 2014	Lower esophageal sphincter resting pressure (LOS-RP) (mmHg)	16±3	21±1	0.08	Lower (trend) LOS-RP
Grande *et al.* 1999	LOS-RP (mmHg)	11-25	16-38	< 0.001	Lower LOS-RP
Ferrioli *et al.* 1998	LOS-RP (mmHg)	35±9	31±14	NS	Similar LOS-RP
Nishimura *et al.* 1996	LOS-RP (mmHg)	15[8;27]	11[4;16]	NS	Similar LOS-RP
Dysphagia Patients					
Besanko *et al.* 2011	LOS-RP (mmHg)	23±4	15±1	< 0.05	Higher LOS-RP
Andrews *et al.* 2008	LOS-RP (mmHg)	26±4	17±2	0.03	Higher LOS-RP
Robson *et al.* 2003	LOS-RP (mmHg)	33.3	32.5	NS	Similar LOS-RP
Lower (o)esophageal sphincter (LOS) relaxation					
Healthy Volunteers					
Besanko *et al.* 2014	IRP4 (mmHg)	4±1 (Right Lateral) 7±1 (Upright Liquid) 8±1 (Upright Solids)	3±1 (RL) 3±1 (UL) 4±1 (US)	NS <0.01 <0.001	Decreased LOS relaxation (Upright)
Dysphagia Patients					
Nakato *et al.* 2017	IRP4 (mmHg)	14[8-27]	17[9-30]	NS	Similar LOS relaxation
Besanko *et al.* 2011	Nadir LOS pressure (mmHg)	2.3±0.6	0.7±0.6	< 0.05	Decreased LOS relaxation
Robson *et al.* 2003	Proportion complete relaxation (%)	24/53 (45)	23/53 (43)	NS	Similar LOS relaxation

Oesophageal Contractility					
Healthy Volunteers					
Besanko *et al.* 2014	Peak P (mmHg) DCI (mmHg.cm.s)	38±9 835±260	41±8 947±201	NS NS	Similar peak pressure and DCI
Grande *et al.* 1999	Distal amplitude (mmHg)	40-77	56-158	< 0.001*	Lower mean distal amplitude
Ferrioli *et al.* 1998	Contractile amplitude (mmHg)	97±41	107±35	NS	Similar mean distal amplitude
Nishimura *et al.* 1996	5cm above LOS (mmHg)	37[20;54]	114[58;142]	< 0.05	Lower mean distal amplitude
Dysphagia Patients					
Nakato *et al.* 2017	DCI (mmHg.cm.s)	1005[350;2063]	464[218-1227]	NS	Similar DCI
Besanko *et al.* 2011	Peak P (mmHg)	54±8	62±6	NS	Similar peak pressure and DCI
Robson *et al.* 2003	Contractile amplitude (mmHg)	71	74	NS	Similar mean distal amplitude
Oesophageal Peristalsis (Success)					
Healthy Volunteers					
Nishimura *et al.* 1996	Percent successful peristaltic contractions (%)	80 [60;100] Liquids	100[90;100) (L)	<0.05	Decrease in successful peristalsis
Dysphagia Patients – no data					

2.3.3.3 Study quality and bias

Quality of six diagnostic studies (one pharyngeal, four esophageal and one in both) between older and young cohorts is summarized in Table 2.13. No study achieved more than a moderate quality or strength of recommendation for diagnostic manometry in older people. The risk of bias in studies of esophageal or pharyngeal manometry in healthy volunteers/ patients was considered low overall.

Table 2.13 Quality and Strength of Recommendations for Diagnostic Manometry

Study	Comparative Diagnostic	GRADE recommendation
Pharyngeal Studies in Dysphagia Patients		
Ribeiro *et al.* Esophageal Manometry: A Comparison of Findings in Younger and Older Patients. *Am J Gastroenterol* 1998; 93:706-710.	Increase in abnormal studies	2B
Meier-Ewert HK *et al.* Effect of Age on Differences in Upper Esophageal Sphincter and Pharynx Pressures Between Patients With Dysphagia and Control Subjects. Am J Gastroenterol 2002; 96:35-40.	Different mechanism	2B
Oesophageal Studies in Dysphagia Patients		
Nakato *et al.* Age-Related Differences in Clinical Characteristics and Esophageal Motility in Patients with Dysphagia. *Dysphagia* 2017; 32:374-382.	Major diagnosis in 39 vs 28%	2B
Shim *et al.* Effects of Age on Esophageal Motility: Use of High-resolution Esophageal Impedance Manometry. *J Neurogastroenterol Motil* 2017; 23:229-236.	Similar numbers	2C
Andrews *et al*. Age and gender affect likely manometric diagnosis: Audit of a tertiary referral hospital clinical esophageal manometry service. *J Gastroenterol Hepatol* 2009; 24:125-128.	Increase in abnormal studies	2C

Robson & Glick. Dysphagia and Advancing Age. Are Manometric Abnormalities More Common in Older Patients? *Dig Dis Sci 2003*; 48(9): 1709-1712.	High proportion achalasia	2B
Ribeiro *et al.* Esophageal Manometry: A Comparison of Findings in Younger and Older Patients. *Am J Gastroenterol* 1998; 93:706-710.	Increase in abnormal studies	2B

2.3.4 Discussion

Most pharyngeal high-resolution manometry (P-HRM) studies describe lower UOS resting pressure (tone) in older persons, compared to the young. This would be in keeping with the anatomical descriptions of increased fibrofatty infiltrates in the cricopharyngeus muscle in older persons (Cook et al. 1992). This less compliant, more fibrotic, and less muscular UOS would not impart the same tonic pressure on the manometry catheter. One would also expect this less compliant sphincter to relax and open to a lesser extent. While some studies were in keeping with reduced UOS relaxation or increased residual pressures, in older persons, this was not universally reported. There was also some variability in the measured duration of UOS relaxation. These findings are complex to interpret due to inter-individual variability, differing measurement and analysis technologies and the known influence of bolus volume and viscosity on these parameters. We tried to account for the challenge by reporting values for 5ml liquid boluses only.

When considering pharyngeal contractility, while some studies showed increased peak pressures in older, as compared to younger healthy volunteers, many other studies did not replicate these findings. In fact, some studies, including using high-resolution manometry showed a decrease in contractility in older persons (Yoon et al. 2014). While it is conceptually appealing to postulate increased hypopharyngeal peak pressures secondary to downstream

resistance, data confirming this are limited. Therefore, the effects of ageing on pharyngeal contractility remains unclear.

Few studies have reported on hypopharyngeal intrabolus pressures (IBP), a known marker of UOS-flow restriction (Pal et al. 2003). This likely relates to the technical challenge of measuring IBP. The study by Kern et al. (Kern et al. 1999), using videomanometry, demonstrated a higher hypopharyngeal IBP in older persons, comparing to younger healthy volunteers.

In the oesophagus the findings were inconsistent with most studies showing no changes and a small number showing decreased LOS relaxation and reduced distal oesophageal contractile amplitudes. Overall, there was no convincing evidence of any distal oesophageal changes in older patients. Some studies have shown increased diagnosis of achalasia or spastic motility disorders but again the evidence was conflicting with most studies reporting no change. A more critical analysis of these studies reveals marked variability in the definition of older persons with the cut-off, even among the reported studies, varying between 60 and 80 years of age.

The descriptions of changes occurring at the lower oesophageal sphincter are intriguing. One group has described apparently reduced LOS relaxation in several studies, in both older healthy volunteers and patients. This is in contrast with the study by Grande et al. (Grande et al. 1999) which described reduced pressures in the LOS in older patients. A study by Jung (Jung et al. 2015) is one of the few using high resolution manometry, and while not included in this review as their definition of older age was over fifty years of age their study did also show reduced LOS relaxation in ageing, using high-resolution manometric metrics. A recent study by Djinbachian et al. (Djinbachian et al. 2021) described a correlation between age and the integrated relaxation pressure (IRP4) at the LOS, adding some further weight to the notion of reduced LOS relaxation in older persons.

Some authors have described the oesophageal changes in some older patients as typical of that seen in intercurrent conditions and question an overt condition of presbyesophagus (Tack & Vantrappen 1997). While some current studies report findings that would fit with the original description of presbyesophagus, others do not show these changes. Very few studies have reported on the proximal oesophagus. A study by Dantas et al (Dantas et al. 2010) did not show changes in the proximal oesophagus with ageing but this study has to be considered with care due to the relatively low age cut-off used.

Numbers of healthy volunteers and even older patients are relatively limited in most of the reported literature. The reasons for this are not entirely clear but may potentially represents under-referral of older persons for manometry studies, perhaps due to clinicians' perceptions that dysphagia is part of normal ageing. The reality may be that some with treatable underlying pathologies may be missing out on treatments for this reason.

In summary, existing studies provide some evidence of an impairment of UOS function (manifest as reduced relaxation) in older persons. It is not clear at what age this impairment develops but it seems to be present in the description of cohorts over 65 years of age. There is some contention whether there is an accompanying increase in pharyngeal contractility, postulated as a compensatory mechanism. The data on oesophageal contractility and motility disorders are conflicting with some studies suggesting decreased LOS relaxation may also occur in older healthy volunteers, as well as patients. Some studies show an increase in achalasia.

Chapter 3 Theories, Hypotheses and Aims

3.1 Theories underpinning the research program presented in this thesis

> *In theory, there is no difference between theory and practice, while in practice, there is. – Benjamin Brewster*

Fries (Fries 1980) described a compression of senescence as an increase in the proportion of individuals surviving into their eighties and nineties increasing over time towards the ideal survival curve (Figure 3.1). This is particularly pertinent to Australia, which enjoys one of the highest life expectancies in the world. In 2018, the combined life expectancy at birth (males and females) was 82.8 years of age (AIHW 2022).

Importantly, however, it is critical that quality of life, functionality, and participation in activities that enable enjoyment of the increased lifespan are also retained (WHO 2016). While we know that swallowing function declines with age, with potentially detrimental consequences such as dysphagia, malnutrition, dehydration, or pulmonary aspiration (Clavé & Shaker 2015, Rommel & Hamdy 2016), we know little of the biomechanics underlying age-related swallowing function and dysfunction, the topic of this research program.

Prevailing theories of age-related organ system functional decline are settled on two theories: a slowly progressive linear change, which manifests as dysfunction below a certain threshold (Shock 1960, Strechler & Mildvan 1960, Fried et al. 2001) or a stepwise decline in function due to accumulated deficits (Rockwood & Mitnitski 2007). While linear decline can be demonstrated, for example, for a decline in renal function over time (Fries 1980), the pattern of swallowing function decline is less clear, as there is no single measure of swallowing function by which to measure declining organ function.

Presbyphagia, or normal or expected, age-related swallowing impairment, had been described as a phenomenon that occurs in the late eighties and nineties (Soergel et al. 1964). As a concept, presbyphagia remains controversial in terms of whether it represents true age-related changes or occurs as the result of intercurrent illnesses (Tack & Vantrappen 1997). This is relevant, as chronic diseases such as cardiovascular disease with potential risk for strokes, diabetes mellitus with accompanying neuropathies, and neurodegenerative diseases such as Parkinson's and Motor Neurone Disease, all increase with age. Conceptually, this fits best with the accumulated deficits model of ageing, described above.

Furthermore, from the existing literature, there is evidence that sensory and motor neurodegenerative changes are associated with ageing and are also known to occur in some age-related diseases. Changes relating to sensory and motor neurodegeneration have been demonstrated in the upper gastrointestinal tract in animals (Johnson et al. 1998, Cowen et al. 2000) and humans (Phillips et al. 2003, Camilleri et al. 2008). Intercurrent medical conditions affecting sensory or motor function and/or age-related neurodegeneration may both contribute to changes in swallowing biomechanics. The exact manifestations of such changes across the lifespan are hereto unknown and the subject of this research program.

Novel methodologies focused on high-resolution manometry with impedance and analyses of the interrelationship of pressure and flow (measured as impedance-based bolus distensions) provide us with tools to better understand swallowing biomechanics, in the pharynx and upper oesophageal sphincter (Pharyngo-UOS) and oesophagus and oesophago-gastric junction (Oesophago-OGJ). In Methods (Chapter 4), I will outline high-resolution manometry with impedance, pressure flow analytical methods and its application with aim of applying these methods in measuring swallowing biomechanics in asymptomatic older persons and symptomatic older patients, as follows.

3.2 Hypotheses and Aims

Part II: Asymptomatic Older Persons

Overarching Hypothesis 1: When compared to young controls, *older persons* present with biomechanical changes in swallowing function, objectively quantified using high-resolution manometry with impedance.

Chapter 5 Pharyngo-UOS function in older persons

Hypothesis

Older persons (asymptomatic older healthy volunteers) demonstrate differences in pharyngeal and UOS metrics in keeping with a pattern of reduced UOS relaxation and opening and associated compensatory changes.

Aims

The aim of the study presented in Chapter 5 was to apply the newly developed pharyngo-UOS pressure-topography and flow-analyses to pharyngeal high-resolution manometry impedance to determine differences in metrics related to the 1. pharynx and 2. UOS in asymptomatic older healthy volunteers, comparing to asymptomatic young health volunteer controls.

Objective

In order to test the hypothesis underpinning this study, pharyngo-UOS swallowing function was tested in community dwelling asymptomatic volunteers (n=110), collected across multiple studies, for 5 and 10ml liquid and viscous boluses using high-resolution manometry with impedance. Data gathered were analysed using novel pressure-flow analysis methods to determine biomechanical change in older persons (80 years of age and above) by comparing the data from older persons with that of multiple younger cohorts (in 20-year intervals).

Rationale

Gaining a better understanding of the biomechanically measurable age-related changes in pharyngeal and UOS function provides an important foundation for future research, including establishing a baseline for comparison for the remainder of this research program with the goal of objectively measuring impaired swallowing in older persons with the ultimate aim of targeting interventions to improve quality of life.

Chapter 6 Impaired bolus clearance in asymptomatic older adults during high-resolution impedance manometry

Hypothesis

Older persons demonstrate evidence of impaired oesophageal bolus clearance for increased consistencies, compared to asymptomatic young healthy volunteers.

Aims

The aims of the study presented in Chapter 6 were to use intraluminal impedance methods to characterize upright postural bolus clearance for asymptomatic older persons, compared to young; and to determine the impedance manometric correlates of failed bolus clearance.

Objective

In order to test the hypothesis underpinning this study, data from n=15 older persons (≥ 80 years of age) were compared to that of n=30 young healthy volunteers using established methods of measuring bolus clearance, while measuring novel oesophageal pressure-flow metrics, such as impedance ratio in both groups for the purpose of correlating such metrics with failed clearance.

Rationale

Bolus clearance is an essential function of oesophageal motor function. There is some existing evidence to suggest that oesophageal bolus clearance is reduced even in healthy older persons, especially the older old. It is important to understand how this occurs and what the potential consequences and implications may be, especially for symptomatic older patients. It is also important to understand any associated biomechanical changes in older non-symptomatic persons in order to better contextualise changes observed in symptomatic older persons, by comparison.

Chapter 7 Age-related impairment of esophagogastric junction relaxation and bolus flow time

Hypothesis

Older persons demonstrate reduced lower oesophageal sphincter relaxation, compared to asymptomatic young healthy volunteers.

Aims

The aims of the study presented in Chapter 7 were to evaluate different aspects of oesophago-gastric (OGJ) function in asymptomatic individuals over eighty years of age compared to asymptomatic young controls: 1. OGJ barrier function at rest through the novel metric OGJ-CI; 2. Swallow-induced OGJ-relaxation through integrated relaxation pressure in 4 seconds (IRP4); and 3. OGJ bolus flow through bolus flow time

Objective

In order to test the hypothesis underpinning this study, data from n=15 older persons (≥ 80 years of age) were compared to that of n=30 young healthy volunteers using both established methodology of determining lower oesophageal sphincter relaxation but also adding novel methods of OGJ-barrier function.

Rationale

While some studies have shown reduced LOS relaxation in older persons, findings on OGJ barrier function have been conflicting. In order to interpret patient studies, we need to better understand OGJ-function in asymptomatic older persons, particularly if there potentially are abnormalities relating to age. Furthermore, abnormalities at the OGJ will influence pressure-flow measurements and distention pressures in the oesophagus, therefore, is essential to understanding any potential biomechanical changes in the oesophageal body in ageing in both asymptomatic and symptomatic older persons.

Currently there are no studies of longitudinal interval changes in pharyngo-UOS or oesophago-OGJ. As this research program has occurred over several years and many asymptomatic individuals volunteered for multiple studies, including through an amendment to an original study to collect normative data on healthy volunteers (described in Chapter 5), repeat studies were collected on a proportion of asymptomatic young and older persons. Where equipment with the same technical specifications were used, this enabled us to compare data at an interval of several years apart in multiple individuals. As nothing is known about how biomechanical changes may progress with age, and with increasing inter-individual differences occurring, the repeat measurements provided a unique opportunity to assess interval changes, measured in the pharyngo-UOS and oesophago-OGJ in Chapters 9 & 10:

Overarching Hypothesis 2: Biomechanical changes observed in the pharyngo-UES and/or oesophago-OGJ in older persons change over the lifespan and reach a threshold in keeping with impaired function bordering on failed function in the ninth decade of life.

Chapter 8 Interval Change in Pharyngo-UOS and Oesophago-OGJ in older persons

Hypotheses

1. Reduced UOS relaxation and a compensatory increase in hypopharyngeal contractility, occurs in older persons, and these changes progress over time.
2. Oesophago-gastric junction dysfunction, reduced contractility and reduced bolus clearance occur in older compared to younger persons, and a further increase in these changes occurs only within the older group.

Aims The aims of the study presented in Chapter 8 were to measure interval change in pharyngo-UOS and oesophago-OGJ biomechanics in asymptomatic young and older persons, and changes between baseline and follow-up studies in both groups.

Objective

In order to test the hypothesis underpinning this study, paired P-HRM-I studies in 18 younger (21-79 years of age) and 10 older persons (≥ 80 years of age) were compared at a median interval of 4-6 years.

Rationale

A better understanding of interval change in swallowing biomechanics will increase understanding related to intercurrent illness and changes in symptomatic older patients and may also help guide future community-based, preventative interventions to improve health outcomes. This will also help inform our understanding of changes in swallowing function across the lifespan to assist in modelling swallowing function decline.

Part II represents a comprehensive assessment of swallowing biomechanics, based on high-resolution manometry with impedance, in older persons. This lays important groundwork for the context of symptomatic older patients, enabling us to compare their swallowing function

with both with an extensive cohort of younger controls but, importantly, also with age-matched controls in an attempt to assess any additional biomechanical changes.

Part III – Symptomatic Older Patients

Overarching Hypothesis 3: Older persons with symptomatic dysphagia (termed *older patients*) have additional biomechanical changes to that observed in asymptomatic older persons.

Chapter 9 Pharyngeal High-Resolution Manometry with Impedance (P-HRM-I) in Older Patients

Hypothesis

Older patients have additional abnormalities on P-HRM-I compared to age-matched controls.

Aims

The aims of the study presented in Chapter 9 were to: 1. determine which P-HRM-I derived metrics distinguish older patients from younger and age-matched controls, 2. Assess novel pharyngeal pressurization patterns in older patients, and where available, 3. assess radiology for evidence of swallowing dysfunction in terms of pulmonary aspiration and significant pharyngeal residue

Objective

In order to test the hypothesis underpinning this study, data from P-HRM-I studies, and where available, radiology studies, were compared in 47 older patients (≥ 80 years of age) with 20 older controls, 454 younger patients and 101 younger controls.

Rationale

As asymptomatic older healthy volunteers have evidence of UOS restriction, change in older patients would have to represent a quantum change in this restriction, or added abnormalities

to explain symptoms. Understanding such change will improve our understanding of the genesis of pharyngeal symptoms and will help guide treatments including interventions in older patients with oropharyngeal dysphagia.

Chapter 10 Increased prevalence of major oesophageal motor disorders and impaired bolus clearance in symptomatic older patients

Hypothesis

Major oesophageal motility disorders occur more frequently in older patients and motility disorders are associated with poor oesophageal bolus clearance in older patients

Aims

The aim of the study presented in Chapter 10 was to describe oesophageal motor disorders in older patients, using the Chicago Classification, and disorders associated with symptoms. A second aim was to determine whether there were observable differences in pressure-topography metrics between older and younger patients.

Objective

In order to test the hypothesis underpinning this study, data from n=1185 patients who underwent HRM-I were analysed using the Chicago classification of oeosphageal pressure topography, and through analysis of impedance-based bolus clearance. Subgroup analysis was done by referral symptoms for patients 80 years of age and older (n=91)

Rationale

Older patients are less often referred for motility studies as their younger counterparts, despite the fact they may present later in the cause of a motility disorder due to decreased sensory perception or minimalization of their own symptoms. Better understanding of motility disorders

in older patients may provide insights into how such older patients can be better clinically triaged and treated to achieve improved outcomes and quality of life.

Chapter 11 Oesophageal pressure flow analysis, correlation of oesophageal metrics with age

Hypothesis

Pressure-flow analyses of oesophageal HRM-I data will reveal abnormalities distinguishing older patients form controls, even when pressure topography does not reveal differences.

Aims

The aims of the study presented in Chapter 11 were to compare symptomatic older patients (80 years of age and older) with age-matched controls, younger patients, and young controls; assess multiple rapid manoeuvres in older patients with weak contractility and correlate age with HRM-I metrics.

Objective

In order to test the hypothesis underpinning this study, oesophageal pressure-flow analysis was undertaken on older patients (n=106), matched to younger patients with a similar diagnosis. Both groups were age-matched to asymptomatic controls.

Rationale

Asymptomatic older persons have impaired oesophageal contractility and bolus transport. The pathophysiology of oesophageal symptoms is mostly unknown and to date oesophageal pressure topography has not consistently been correlated with symptoms. Oesophageal pressure-flow analysis may help identify abnormalities that distinguish older patients from age-matched controls to better understand oesophageal physiology, as relates to age, and potential for interventions or treatments

In summary, this research program has several overarching aims with the purpose of understanding the interrelationship between pharyngo-UOS, and oesophago-OGJ biomechanical motor function, physiological function (safe, effective bolus transport) and symptoms in older persons. I hypothesise measurable changes in older persons and increased and/or additional changes in older patients. Understanding the underlying biomechanics of any observations will help guide potential therapeutic interventions.

Chapter 4: Methods

> "Much of outcomes research is a systematic attempt to exploit what is known and make it better." ~ Kevin Kelly

4.1 Introduction to Methods

The methods section covers methods related to computer-based analyses of high-resolution manometry and impedance in the pharynx (pharyngeal high-resolution manometry with impedance: P-HRM-I), oesophagus (referred to as high-resolution manometry with impedance: HRM-I), and additional investigations used for triangulating data with clinically relevant outcomes, e.g., radiology.

Analysis evolved over the duration of the research program. Where practical, data gathered early during the research program was re-analysed using the latest iteration of analytics on the online analysis platform Swallow-Gateway (swallowgateway.com), hosted by Flinders University.

Subchapters 4.2 and 4.3 thus describe the principles underlying pressure-flow analysis in the pharynx (4.2) and oesophagus (4.3). Where necessary some more detail on technical aspects of other analyses (e.g., pressure topography) is included in further chapters.

A standardized methodology had been followed in the laboratory for the period covered in studies included here, which will be described in subchapter 4.2.

4.2 Pharyngeal Pressure-Flow Analysis: Procedures, Analysis and Metrics

4.2.1 Laboratory Procedure

Subjects were telephonically interviewed for the presence of any gastrointestinal symptoms, including dysphagia and gastroesophageal reflux disease, medical illnesses, hospitalisations and medications. Subjects were excluded from studies if they had any symptoms, a history of upper gastrointestinal surgery, diseases associated with gastrointestinal motor disturbances, including uncontrolled diabetes mellitus (with the exception of studies in symptomatic patients described in chapters 9, 10 and 11). Subjects were also asked to hold all medications which may influence gastrointestinal motor function for 24-48h or excluded if they could not do so.

Subjects were then required to attend for a manometry study after overnight fast. On arrival they completed a modified version (scale reversed) of a swallowing function questionnaire validated against measured eating behaviour (Dakkak & Bennett 1992) and/or the Sydney Swallow Questionnaire (Wallace et al. 2000, Szczesniak et al. 2014). For later studies brief esophageal dysphagia questionnaire - BEDQ (Taft et al. 2016) and GERD-Q (Jones et al. 2009) were also completed. In addition, subjects completed laboratory specific questionnaires (a visual analogue scale 10cm long) on the severity of symptoms of dysphagia, heartburn, regurgitation and documented any weight loss in the preceding 6 months.

Manometry studies were all undertaken with the Medical Measurement System GI Solar equipment (Laborie, Enschede, Netherlands) using various solid-state catheters (Unisensor, Laborie, Attikon, Switzerland), with diameter 2.8mm or 3.2mm and sensor arrays spanning 25, 32 or 36cm. All catheters used had identical unidirectional pressure sensors spaced at 1cm apart. All catheters had between 12 (25cm) and 16 (32/36cm), 2cm length impedance segments. For the normative data described in Chapter 5, reference is made to the 3.2mm catheter diameter values. Data were recorded at 20Hz.

For placement, the catheter was inserted through an anaesthetised nostril (2% lignocaine gel) to straddle the pharyngo-oesophageal segment and the patient was given time to

accommodate for a minimum of two to five minutes. For the recording in the pharynx the catheter was positioned from above the velopharynx to below the oesophageal transition zone (Figures 4.1 and 4.2).

Standardized boluses were administered in a sitting posture with head held in neutral position: 5ml and 10ml normal (0.9%) saline as a liquid bolus (Level=0 on the IDDSI scale) and a standardized viscous bolus (Level=4 on IDDSI; Sandhill Scientific, Denver, US for earlier studies prior to c 2016; and Trisco Foods, Brisbane, Australia for later studies 2016-currently). Intervals of 20-30s were allowed between bolus challenges to allow for the bolus to pass into the stomach (Vanek & Diamant 1987, Tutuian et al. 2004). For some studies additional solid boluses (2x2cm, Saline-soaked bread Level= 7 on IDDSI) were given at 30 sec intervals. Subjects were asked to mark their bolus perception for viscous and solid boluses on a visual analogue scale which consisted of a 10-cm-long line marked at 0 cm (0cm = “none”, 10 cm = “stuck/pain.”)

Following completion of the study the study subjects were given refreshments and observed for an hour prior to being discharged home.

4.2.2 Data analysis of Pharyngeal Pressure-Flow Analysis

Complete data were exported from the MMS GI Solar Manometry Recording system as American Standard Code for Information Interchange (ASCII) files and subsequently imported onto the online software analysis platform Swallow-Gateway (swallowgateway.com), which is owned by Flinders University and Flinders Partners.

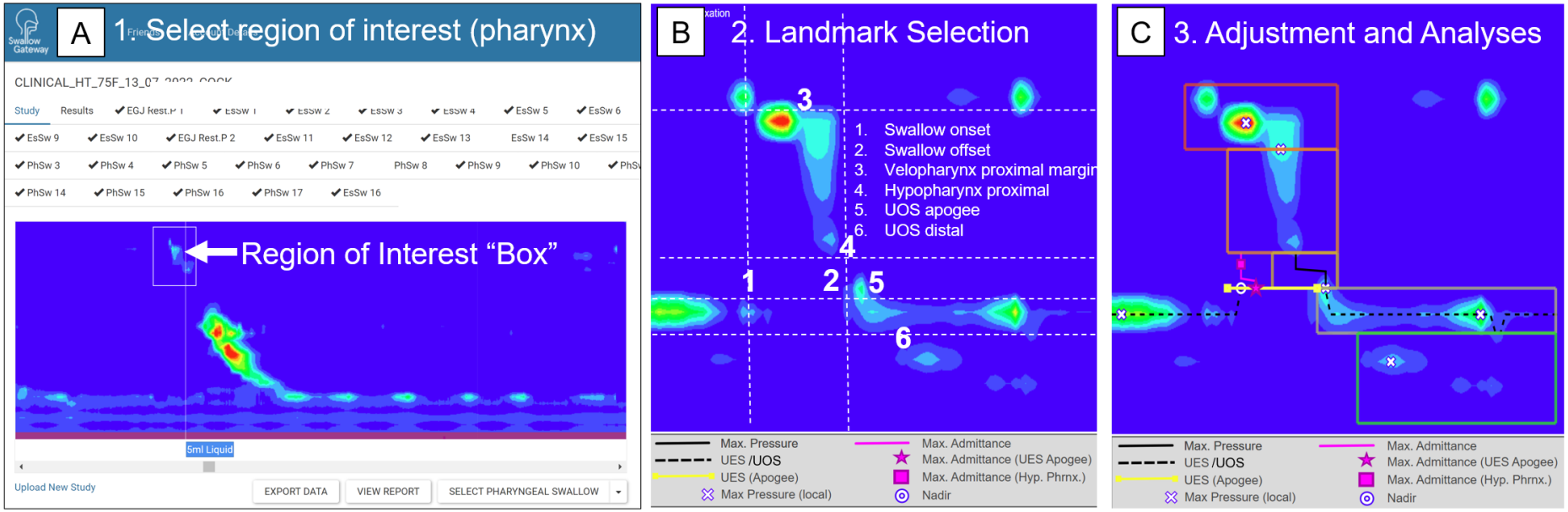
Analyses via swallowgateway.com depends on the selection of a region of interest encompassing either; 1. pharynx, 2. oesophagus or 3. oesophagogastric junction. This

chapter includes descriptions of pharyngeal and oesophageal region analyses, while oesophago-gastric junction analysis is described elsewhere (Chapter 7).

Pharyngeal analysis using swallowgateway.com is described in Figures 4.1 and 4.2. As a standardized approach, core outcomes set metrics, agreed to by a High-Resolution Pharyngeal Manometry International Working Group, are reported on (Table 4.1)

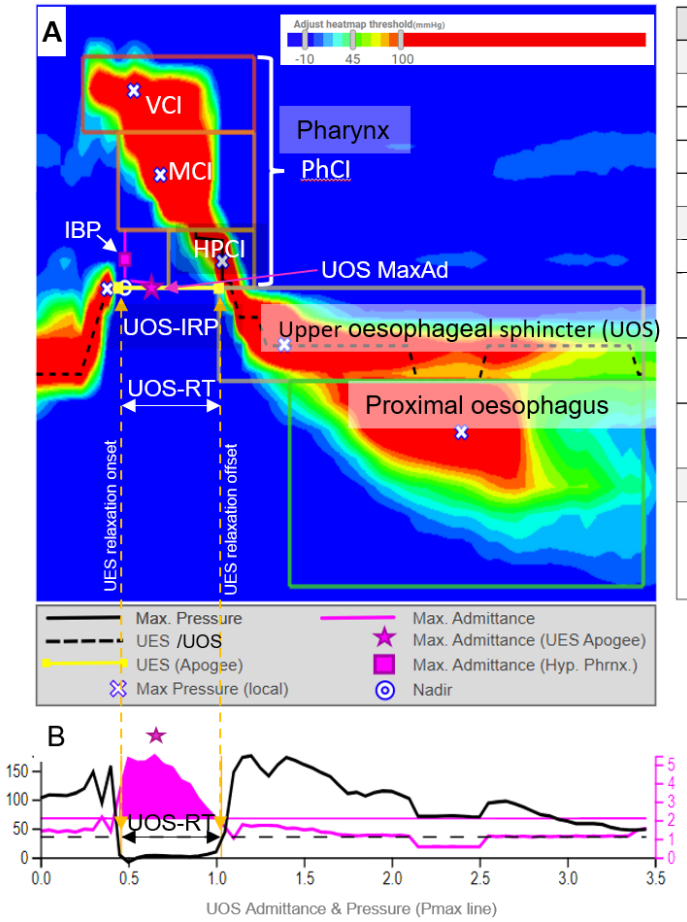
Table 4.1: Consensus Metrics for High-Resolution Pharyngeal Manometry (HRPM)*		
Pharyngeal Lumen Occlusive Pressures		
PhCI (mmHg.s.cm)	Pharyngeal Contractile Integral (CI)	Global measure of pharyngeal contractile vigour in space-time box from upper border velopharynx to upper margin UOS.
VCI (mmHg.s.cm)	Velopharyngeal CI	Contractile vigour velopharyngeal region
MCI (mmHg.s.cm)	Mesopharyngeal CI	Contractile vigour mesopharyngeal region
HCI (mmHg.s.cm)	Hypopharyngeal CI	Contractile vigour hypopharyngeal region
Hypopharyngeal Intrabolus distension pressure		
IBP (mmHg)	Hypopharyngeal intrabolus pressure	Hypopharyngeal IBP at 1cm above the UOS apogee at time of maximal distension deduced from
Upper oesophageal sphincter UOS/UES relaxation and opening		
UOS IRP (mmHg)	UOS integrated relaxation pressure	Measure of extent of UOS relaxation. Median of lowest non-consecutive 0.2-0.25s e-sleeve pressure at UOS
UOS RT (sec)	UOS relaxation time	Duration of UOS relaxation below 50% baseline and return
UOS Max Ad (mS)	UOS maximum admittance	Extent of UOS opening cross-sectional area
* From Omari et al. High-resolution Pharyngeal Manometry and Impedance: Protocols and Metrics – Recommendations of a High-Resolution Pharyngeal Manometry International Working Group. *Dysphagia* 2019		

Figure 4.1 Pharyngeal pressure-flow analysis using Swallow-Gateway (swallowgateway.com)



Swallow-Gateway (swallowgateway.com) displays the study as recorded including all marked swallows (Fig 4.1A). Display and methods are uniform regardless of the system used to record the initial data. A region of interest (pharynx, oesophagus, or oesophago-gastric junction) is selected (Fig 4.1A). The pressure topography is displayed, and landmarks selected (Fig 4.1B). The landmarks for the pharynx are: 1. Swallow onset, 2. Swallow offset, 3. Velopharynx proximal margin, 4. Hypopharynx proximal margin, 5. Upper oesophageal sphincter (UOS/UES) apogee, and 6. UOS/UES distal margin. Subsequently landmarks can be adjusted by dragging the edges of boxes or changing timing onsets (Fig 4.1C). Analyses are calculated and displayed in a panel but can also be exported as a Microsoft Excel™ file.

Figure 4.2 Pharyngeal pressure topography and pressure-flow analysis. This example is a 5ml swallow from a 40-year-old control.



C. Pharyngeal Metrics		
Contractility		
VCI	Velopharyngeal contractile integral	Pressure*length*duration at velopharynx
MCI	Mesopharyngeal contractile integral	Pressure*length*duration at mesopharynx
HPCI	Hypopharyngeal contractile integral	Pressure*length*duration at hypopharynx
PhCI	Pharyngeal contractile integral	VCI+MCI+HPCI
Upper Oesophageal Sphincter (UOS)		
UOS IRP	UOS integrated relaxation pressure	Pressure for lowest 0.25sec at UOS
IBP	Intrabolus pressure	IBP in hypopharynx at 1cm above UOS apogee at maximal UOS opening distension
UOS-RT	UOS relaxation time	Duration of UOS drop below 50% to reconstitution above 50%
UOS MaxAd	UOS maximum admittance	Maximal UOS cross sectional area/distension as inverse of impedance (admittance)
Composite Measure of Deglutitive Aspiration Risk		
SRI	Swallow Risk Index	$SRI = \frac{\text{Bolus Presence Time (HP) x IBP (HP)}}{\text{HP Peak P (mean) x Distention-Contraction}}$

Figure 4.2. Pharyngeal swallowing metrics for high-resolution pharyngeal manometry with impedance (P-HRM-I). Pharyngeal pressure topography is shown (Fig. 4.2A) with associated UOS pressure (black) and admittance (purple) (Fig. 4.2B). Regions of interest (orange boxes0 are used to calculate velo-, meso-, and hypopharyngeal contractile integrals. Collectively these form the pharyngeal contractile integral (PhCI), Measures of upper oesophageal sphincter relaxation (UOS IRP), duration of relaxation (UOS-RT), and maximum extent of distention/opening (UOSMaxAd) are shown. International working group metrics (Omari et al. 2020) are shown (Fig. 4.2C).

4.3. Underlying Principles, Metrics Derived and Clinical Utility of Oesophageal Pressure-Flow Analysis

4.3.1 Introduction

We perform oesophageal motility studies to better understand oesophageal physiology, explain patient symptoms such as dysphagia or non-cardiac chest pain, or for the further evaluation of and pre-operative assessment of gastroesophageal reflux disease. In the modern context, such assessments are performed using high-resolution manometry with closely spaced, highly sensitive pressure sensors along a naso-gastrically inserted catheter. The addition of impedance segments allows for the assessment of bolus distension and transit, of conductive boluses, the originally proposed use of impedance during motility studies. This review will focus on added impedance derived metrics, to better understand the relationship of pressure-flow phenomena to patient symptoms.

Oesophageal primary peristalsis is triggered centrally within the brainstem as part of a pharyngeal swallow response, or reflex initiation of secondary peristalsis. The purpose of the oesophageal component of the swallow response is to continue the transport the bolus through the length of the oesophagus and esophago-gastric junction into the stomach. Manometry measures a contraction wave moving distally through the oesophagus. Importantly though, a wave of inhibition (distension) precedes this excitation (contraction). Bolus distension waves are not measured by manometry and requires imaging or impedance to visualize.

In addition to central triggering of inhibition, bolus-induced distension further reactivates a secondary wave of inhibition ahead of, and excitation behind, the bolus, (Patterson et al. 1991, Mittal et al. 2006) as part of a peripheral mechanism, akin to a peristaltic reflex more correctly described as a neuromechanical loop (Costa et al. 2013, Dinning et al. 2014, Spencer et al.

2016). As the peripheral motor pathways are triggered in response to a change in circumferential wall tension generated by the bolus stimulus, they are therefore influenced by factors that change bolus flow and intrabolus distension forces (e.g., posture, viscosity) and luminal radius (e.g., wall compliance). The peripheral mechanism is most important for successful bolus transport of viscous and solids, which do not flow by gravity alone and need to be pushed through the distal oesophagus and sphincter into the stomach.

Currently, oesophageal motility disorders are diagnosed using the Chicago Classification which is a pressure-only characterisation of distal oesophageal contraction and lower oesophageal sphincter relaxation. Impedance-based bolus clearance is assessed as an adjunct. Abnormalities of bolus flow and distension that preceded contraction are not currently classified.

Using methodologies that we have termed pressure-flow analysis (PFA), it is possible to assess bolus flow and related intrabolus pressure (distending force) by combining impedance with pressure data. This provides and additional layer of potentially clinically relevant information. The initial embodiment and description of this methodology was based on intuition; it was hypothesised that the objectivised measurement of bolus flow and associated intrabolus domain forces would provide a sound basis for assessing mechanistically normal and altered oesophageal bolus transport as a means for diagnosing the pathophysiology of oesophageal dysphagia. New data and software improvements have improved our understanding of PFA-derived measures, and this has informed an iterative refinement of the technique.

The purpose of this review of PFA is to provide an update overview of 1) the metrics that can be derived, and 2) the adjunct value of these metrics for defining esophageal neuro-muscular function with a focus on current clinical diagnostic conundrums.

4.3.2 Underlying principles and assumptions of oesophageal PFA

Pressure-flow analysis (PFA) assumes that the intraluminal impedance waveform provides an accurate representation of the bolus domain. That is, impedance records the distension wave that precedes the lumen-occlusive contraction wave, with distension wave properties being determined, for the most part, by neural inhibition and subsequent muscle relaxation. Furthermore, the nadir impedance value of the waveform identifies the most distended part of the bolus domain transiting over in space and time, as well as its maximal cross-sectional area. Based on these assumptions it is possible to map the pressures corresponding to different phases of luminal distension (luminal opening, peak distension and closure) as a bolus transits the length of the esophageal body.

4.3.2.1 Bolus-based distension, and intrabolus pressures

The principles of impedance-based measurements of conductive bolus transiting the oesophagus have been well described and correlated to radiological bolus passage. One observation made during these earlier experiments was that, for an equally conductive bolus and similar voltage, measured electrical current varied depending on the cross-section of the segment adjacent to the paired impedance rings. The maximum extent of distension correlated with the nadir impedance (Silny et. al. 1993). Provided current remains consistent, peak bolus-based distension by a conductive bolus can be deduced from the nadir impedance value recorded. Furthermore, it is now becoming more common to derive the inverse product of nadir impedance (1/Ω) i.e., maximum admittance, as this provides for a linear relationship between the recorded bolus signal (in siemens, S) and luminal cross-sectional area (Kim 2014) (see Figure 4.3).

Intrabolus pressures provide a measure of the sum of propulsive and resistive forces acting on the bolus along its transit through the oesophagus. Successful bolus transit requires that propulsive forces exceed resistive forces, such as the friction between the bolus and oesophageal walls. While intrabolus distension pressures are more or less stable within the centre of bolus domain they increase at the bolus tail prior to luminal closure providing the pressure differential that drives bolus movement.

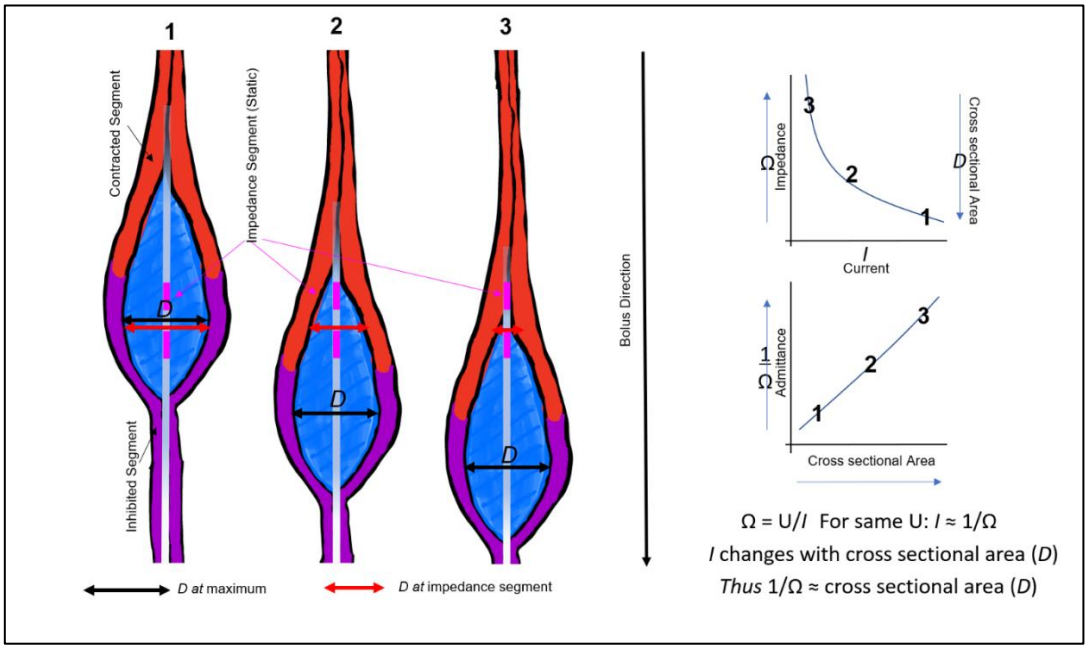


Figure 4.3. Principles behind impedance-based determination of cross-sectional area. Impedance (Ω) equals voltage (U) over current (*I*). Current changes depending on how much bolus it flows through before reaching the oesophageal walls – i.e., varies with cross sectional area (D). As voltage does not change during oesophageal impedance, inverse impedance (admittance) had a linear correlation with cross sectional area. 1-3 represents passage of the bolus (blue) through the oesophagus, with related *relative* measurements displayed on the righthand graphs.

The point of maximal bolus-based distension can be measured as an indication of the centre bolus domain in time and space, intrabolus pressures can also be measured at that peak distension point. This measure of pressure forces recorded at the precise time of maximum bolus distension can also indicate the time of maximum neural inhibition and provides inferences regarding biomechanical properties (passive wall tension and distensibility) that may be one driver of conscious awareness of swallowing, critical to understanding patient symptoms (Cock et al. 2020).

4.3.3 Metrics derived during oesophageal PFA

Metrics derived during oesophageal PFA are based on the underlying principle that impedance-based peak distension identifies the bolus position in space and time relative to oesophageal inhibition and contraction. Metrics focus on: 1. Peak distension time in relation to a. swallow onset and b. contraction. 2 Peak distension area. 3. Peak distension pressure (passive tension at peak distension). 4. Pressure change over time from distension peak to lumen occlusion (passive tension during bolus propulsion), 5. Bolus clearance (Table 4.2). Pressure flow analysis is performed on measurements exported from commercially available high-resolution manometry impedance systems, using the online software Swallow-Gateway (swallowgateway.com) (Flinders Partners, Flinders University, Adelaide, Australia).

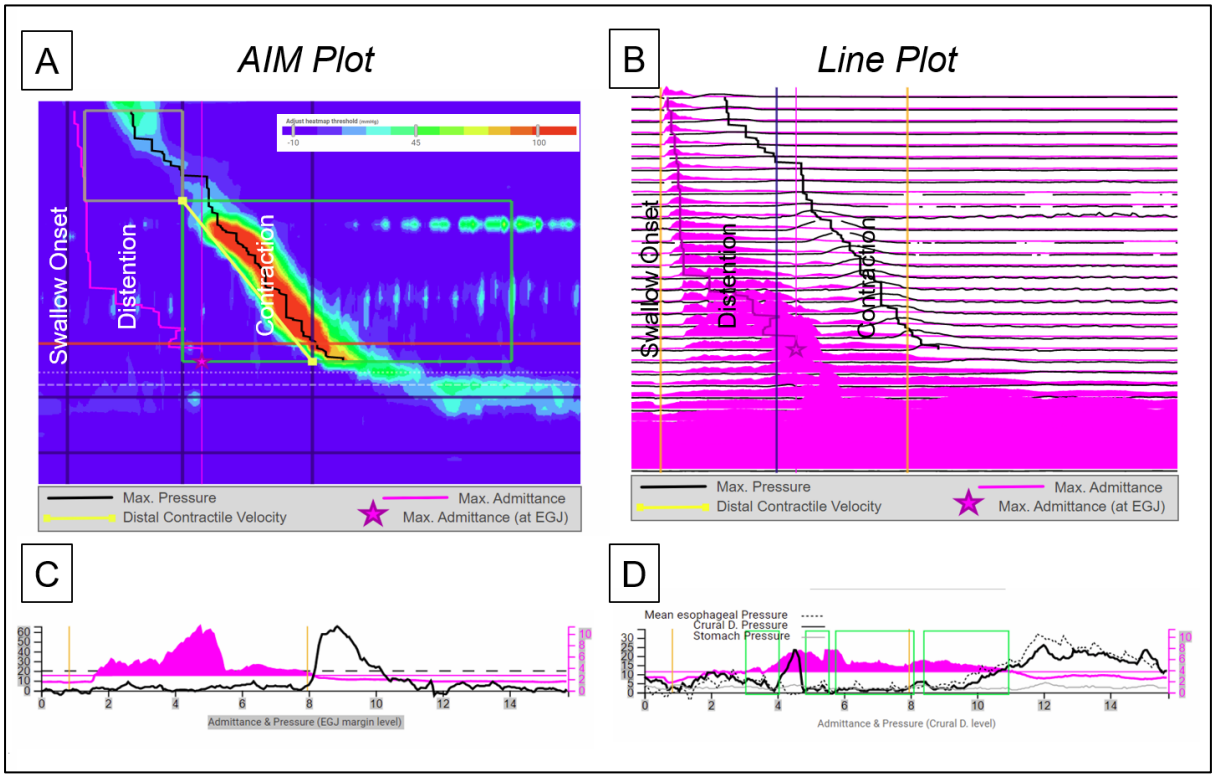


Figure 4.4 Oesophageal pressure-flow analysis (Swallow-Gateway (swallowgateway.com). 4.4A The pressure topography (AIM Plot) representation of swallowing with the indigo line representing maximal distention and black line maximal luminal occlusion. 4.4B Bolus flow is demonstrated to occur through the oesophagus during the inhibitory/distension phase following by clearance by the contraction. Admittance (indigo) and pressure (black) shown at OGJ margin level in 4C and crural diaphragm (CD) level in 4D

Table 4.2 Oesophageal Pressure-Flow Metrics	
Metric	**Technical Description and Interpretation**
Swallow distension latency (SDL in seconds)	Peak distension time in relation to swallow onset
Distension to contraction latency (DCL in seconds)	Peak distension time in relation to lumen occlusive contraction
Peak distension area (maximum admittance in mS)	Impedance-based determination of luminal cross-sectional area measured at/above the OGJ
Peak distension pressure during accommodation (DPA in mmHg)	Mean peak distension pressure (passive tension at peak distension) for the duration of oesophageal accommodation (swallow onset to transition zone)
Peak distension pressure during contraction (DPCT in mmHg)	Mean peak distension pressure (passive tension at peak distension) for the duration of oesophageal contraction (transition zone to contractile deceleration indicating formation of the phrenic ampulla)
Peak distension pressure during emptying (DPE in mmHg)	Mean peak distension pressure (passive tension at peak distension) for the duration of oesophageal emptying (most distal portion from contractile deceleration to top of lower oesophageal sphincter)
Ramp pressure (RP in mmHg.sec).	Changing pressure over time from distension peak to lumen occlusion (passive tension during bolus propulsion)
Impedance Ratio	Ratio of impedance during peak distension (lumen maximally filled with bolus) to that at peak contraction (lumen maximally cleared of bolus) for an individual swallow
Bolus flow time	Duration of bolus permissive pressures at the OGJ

4.3.4 What does PFA add to EPT (physiology/pathophysiology)?

4.3.4.1 Why the need for additional assessment of oesophageal physiology?

The Chicago classification of distal oesophageal motility has created a common language for the description of oesophageal motility disorders. However, by focusing entirely on oesophageal primary peristaltic contraction, the classification system has some shortcomings. Most importantly, the physiological inhibitory mechanisms that influence bolus flow and liminal distension, and in turn the time relationships between swallow, flow/distension and contraction. Without these additional components the picture of oesophageal physiology is incomplete.

This deficiency may well be the reason why, to date, motility studies analysed in the standard fashion have not always correlated well with symptoms and non-obstructive dysphagia (NOD) with a normal motility study have been a particular challenge. Early pressure-flow analysis studies in NOD patients showed elevated intrabolus and ramp pressures during oesophageal emptying, and a shorter time from distal oesophageal distension to contraction, compared to healthy volunteers (Nguyen et al. 2012; Chen et al. 2012). This observation, seen using standard low-resolution manometry recordings, and predominantly with viscous bolus challenges may be suggestive of functional obstruction, possibly due to an underlying disorder of the esophageal inhibition manifesting in the distension, as opposed to the contraction phase of oesophageal bolus transport. Distension, pressure and timing changes may help clarify the pathophysiology and thus potential treatment in these putative disorders.

4.3.4.2 The dilemma of OGJ outflow obstruction as a diagnosis

A diagnosis of OGJ outflow obstruction may prompt initiation of treatments aimed at alleviating the obstruction. Some interventions, such as achalasia balloon dilatation, or per-oral endoscopic or surgical myotomy may irreversibly change the anatomy and function of this important sphincter region. For example, effectively removing the LOS function may expose the individual to gastroesophageal reflux and any related health effects.

The dilemma in the CC diagnosis of this condition is that it relies almost entirely on a determination of a single measured variable influenced by multiple technical challenges, the integrated relaxation pressure in 4 seconds (IRP4). Furthermore, investigators are now directly advised not trust this measure, and to perform adjunct investigations, such as timed barium oesophagram or EndoFLIP to confirm OGJOO. This is because when re-studied after 2 years *without* intervention, many patients with high IRP4s readings normalise (Richter group and one other). It would be of benefit if, rather than relying on additional testing, pressure-flow based metrics could predict clinical outcomes so that a single, inexpensive test would suffice to diagnose clinically relevant outflow obstruction.

Biomechanical studies have identified a pressure differential of 20mmHg as optimal for promoting bolus passage (Nicosia & Brasseur 2002). This is approximately the level of IBP identified by upright as compared to supine studies to identify OGJOO (Quader et al. 2017, Triggs et al. 2019). The interpretation of the above data is that flow resistance during oesophageal emptying increases bolus distension pressures throughout the oesophagus, furthermore the distension pressure ramps up as the clearing peristaltic contraction compresses the bolus against an oesophageal outlet with insufficient opening and compliance. If the bolus distension forces being generated during emptying exceed the lumen occlusive forces generated at the bolus tail, then retrograde bolus escape and bolus residual with result. The progressively increasing distension pressures reflect greater intramural wall tension thus potentially providing a mechanism for generating symptoms during bolus transit. The above seen with liquid and viscous swallows is very likely to be further exacerbated during solid bolus transit.

Pressure-flow analysis of esophageal emptying through the OGJ provides us not only with a better understanding of OGJ bolus flow and clearance, but also explain symptoms as relating to increased intramural tension. Intramural tension increases due to increased peak distension pressure and an accelerated rate of such pressure increase during oesophageal emptying. These data fit logically within our current understanding of the physics involved in traversing

the sphincter region (Nicosia & Brasseur 2002), distal oesophageal distension (Barlow et al. 2002, Jain et al. 2022), and with the genesis of dysphagia as symptom (Cock et al. 2020).

4.3.4.3 Disorders of oesophageal inhibition and other non-Chicago disorders

The contractile response to a loss of inhibition is *earl*ier and more rapid oesophageal contraction, which rather than following and promoting oesophageal bolus transit, may impede it. Within the CC framework, the only non-achalasia inhibitory disorder is distal oesophageal spasm, defined through a short latency period between swallow onset and the contractile deceleration point (formation of phrenic ampulla during oesophageal emptying). The pathophysiology of CC disorders of hypercontractility, type III achalasia and distal oesophageal spasm is not well explained, and such disorders may overlap.

Furthermore, oesophageal pressure-flow analysis appears to show altered flow, distension ramp pressures and relative timing changes in some cases where the CC diagnosis is normal, suggesting potentially undiagnosed inhibitory disorders (Figure 4.5). This raises very important questions around the concept of functional dysphagia. With observable perturbations in pressure and flow related to putative inhibitory disorders, re-assessment of the entire concept of functional dysphagia may be needed.

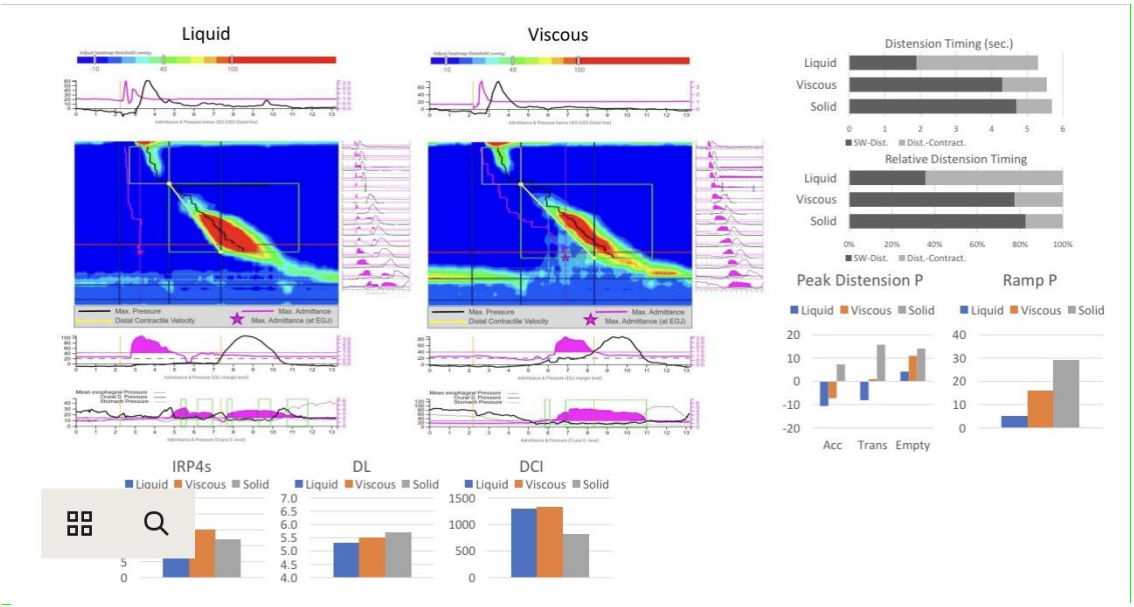


Figure 4.5. Inhibitory disorder on PFA. An example of pressure flow metrics in a 14-year-old with non-obstructive dysphagia and normal motility with daily and severe symptoms demonstrating an increase in ramp pressures with increasing bolus consistency in keeping with rapidly increasing intrabolus pressures to assist bolus transit across the oesophago-gastric junction, and timing changes suggestive of the potential of an inhibitory disorder (data from Prof T Omari used with permission).

4.3.3.4 Dysphagia in Opioid Induced Oesophageal Dysmotility

The use of the mu-opioid agonist remifentanil has been associated with patient-reported dysphagia and the observed effects of this medication are in keeping with opioid induced oesophageal dysmotility (Savilampi et al. 2013, Savilampi et al. 2015, Cock et al. 2017, Cajander et al. 2021). Following administration, rapid distal oesophageal contractions and a shortened duration of LOS relaxation occurred, resulting in increased IRP4.

Cock *et al.* (Cock et al.2017) conducted a PFA analysis following remifentanil and demonstrated oesophageal clearance with a shorter duration bolus flow at the OGJ, a shorter interval between distal oesophageal distension and contraction and higher distension pressures in the distal oesophagus, a biomechanical consequence of the increased flow rates needed for a similar volume bolus to cross the OGJ in a shorter time. Cajander et al. (Cajander et al. 2021) followed up this study using the latest iteration of PFA administering both remifentanil and then reversing peripheral effects by administering methylnaltrexone MNTX), which reversed the OGJ bolus flow effects of remifentanil suggesting such effects occur in the peripheral neural circuits (figure 4.6).

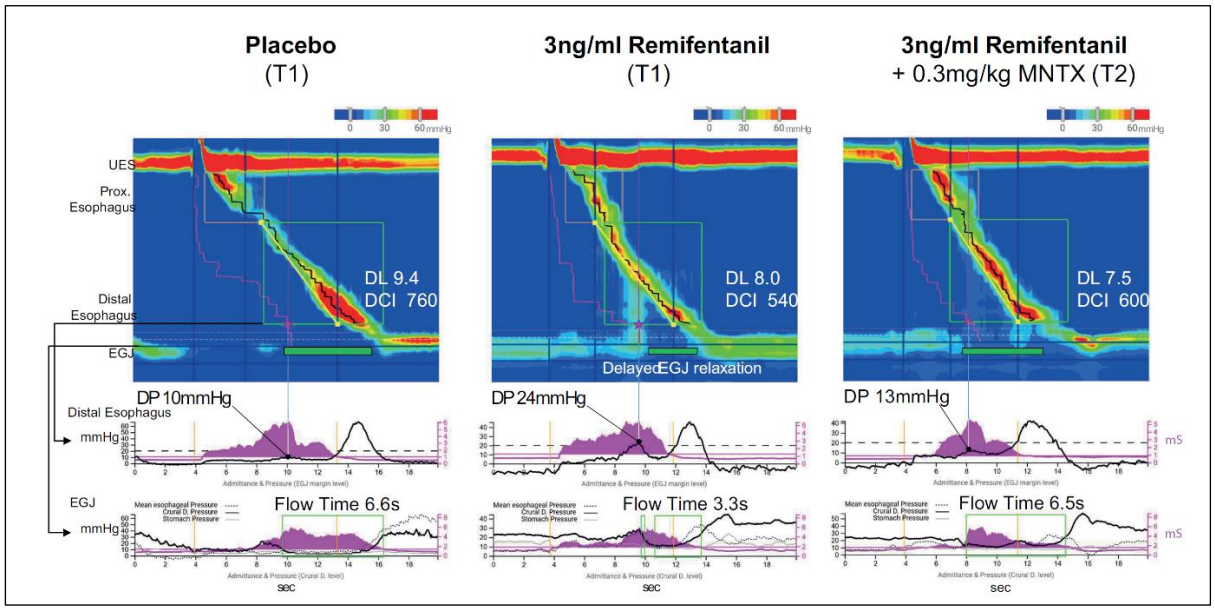


Figure 4.6. OGJ Bolus flow following Remifentanil administration. Oesophagogastric junction at baseline – 6.6 sec, following administration of remifentanil – 3.3 sec and again after administration of methylnaltrexone – 6.5sec (from Cajander *et al*.) demonstrating peripheral opioid effects and reversal.

during oesophageal emptying. Based on these observations, when taken along with observations in other groups, such as esophagogastric junction obstruction above and post-surgical dysphagia (Myers et al. 2012), it is postulated that the observed changes to IBP during oesophageal emptying are relevant to dysphagia as a symptom in these groups.

4.3.4 Summary and Conclusion

The Chicago classification has standardized interpretation of manometry but does not correlate well with symptoms and some disorders are not well explained. Adding pressure-flow analysis adds to the ability of high-resolution manometry impedance in identifying pathophysiology related to oesophageal symptoms with utility in OGJOO and inhibitory disorders. Oesophageal PFA enables us to understand the important bolus transit inhibitory phase of oesophageal physiology. Oesophageal PFA has not been adequately explored in older individuals with fewer symptoms, reduced bolus transit and potentially greater flow resistance at the oesophago-gastric junction.

4.4 Augmented Impedance Methods (Bolus Transit, Mucosal Integrity)

4.4.1 Assessing bolus transit with Impedance

The originally intended use of intraluminal impedance measurement for esophageal motility studies was the qualitative assessment of oesophageal bolus transit rate and clearance. When the impedance catheter is intraluminally in the oesophagus in its resting state, baseline impedance is measured. When a conductive bolus is present across two adjacent impedance electrodes simultaneously, the bolus completes the electrical circuit, and electrical impedance (measured in ohms) drops. As the bolus passes the circuit is broken and impedance returns to its baseline value (Figure 4.7) (Silny et al. 1993, Imam et al. 2005, Hila et al. 2011, Omari et al. 2014).

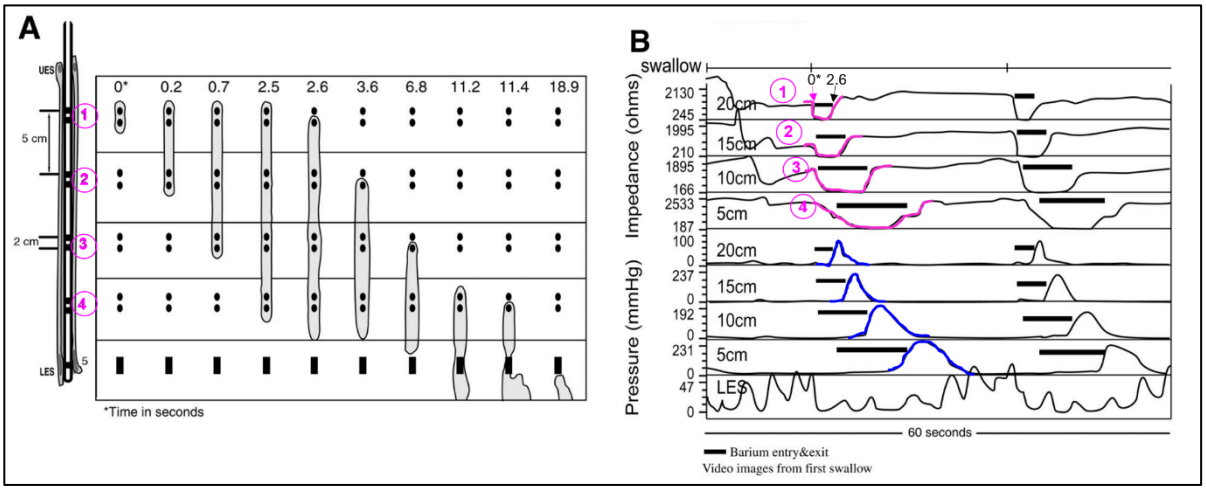


Figure 4.7 Assessment of oesophageal bolus transit. Fig. 4.5A The impedance catheter with four paired impedance rings circled indigo 1-4, set 5cm apart and a cartoon representing bolus transit on radiology. Fig. 4.5B Representation of data for impedance segments 1-4 (circled indigo) and pressure data below (blue) for two swallows. At 0 seconds (0*; indigo arrow) impedance rings 1-2 are connected through conductive bolus, causing impedance to drop, returning to above 50% of baseline at 2.6 seconds (black arrow), representing bolus passage. This pattern is repeated indicating complete bolus transit (Adapted from Imam *et al.* 2005. Included with permission of publisher).

Studies, using simultaneous radiology to assess bolus flow, have demonstrated that bolus passage beyond the impedance segment occurs when impedance from its nadir, returns to above 50% of the baseline value (Sifrim et al. 2004, Imam et al. 2005). Bolus transit can occur both in antegrade (peristalsis) or retrograde (reflux) directions, measurable by determining the directionality of sequential impedance drop along the catheter. In the example in figure 2B, the bolus transits antegradely (distally) down the oesophagus, so that impedance firstly drops, and then returns to level above 50% of baseline, from the most proximal pair of impedance electrodes and sequentially to the most distal electrode pair.

In further healthy volunteer experiments, conducted using combined manometry impedance catheters, a high proportion of complete liquid (L, 97.4%) and viscous (V, 96.1%) bolus clearance was shown to occur for 80% (L) and 70% (V) of swallows (Tutuian et al. 2003). Bolus transit was variable in patient groups but generally complete for those with normal motility patterns, nutcracker oesophagus (as termed at the time), and even for lower oesophageal sphincter abnormalities other than achalasia (Tutuian & Castell 2004). An important, often overlooked, observation from these earlier experiments was that the symptom

dysphagia was often associated with incomplete bolus transit, implying bolus presence likely induces the sensation of dysphagia (Tutuian & Castell 2004). This is an important observation when we consider that the Chicago classification of motor patterns using pressure only has not been shown to correlate well with symptoms (Bogte et al. 2014, Xiao et al. 2014, Lazarescu et al. 2010). By implication assessing bolus transit during motility studies in patients is not only of academic interest but important clinically.

Oesophageal bolus clearance has been shown to occur through the contraction, being above a certain peak value ranging between 20 and 30mmHg, sweeping behind and clearing the bolus tail (Dodds et al. 1972, Kahrilas et al. 1988). Bolus clearance can also be measured by assessing the impedance (or its inverse product admittance) signal before and after peristalsis has swept through the distal oesophagus, based on the principle that the impedance level will only recover to baseline if the bolus clears. By measuring the mean distal oesophageal ratio of impedance at peak distension (lumen maximally filled with bolus) to that at peak contraction (lumen maximally cleared of bolus), an *impedance ratio* (IR) can be measured as a marker of bolus clearance.

Figure 4.8 describes the use of impedance ratio for determining bolus retention.

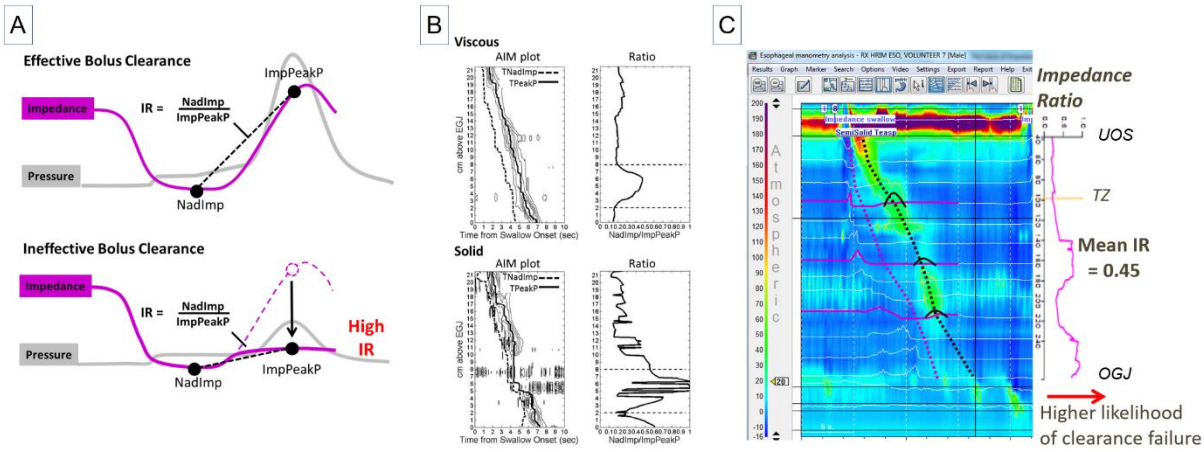


Figure 4.8 Impedance ratio (see description in text). Fig 4.8A & B from Omari et al 2013 (used with permission). Fig 4.8C Example swallow

IR is shown as the ratio of nadir impedance (NadImp) to impedance at peak pressure (Fig 4.8A). An increased ratio demonstrates bolus hold up in this example during viscous and solid bolus swallows (Fig 4.8B). Figure 4.8C shows and example of a weak peristalsis with increased IR occurring in two areas where the peak contractions fail to reach 20-30mmHg (Kahrilas et al. 1988).

IR has been validated in the oesophagus by correlating IR with residual bolus volume on radiology (Omari et al. 2015 – see Figure 4.9 below), thus providing an evidence base for an alternative method of assessing oesophageal bolus clearance based on a continuous variable rather than a dichotomous classification. Similar methodologies based on this principle have been developed by other groups (Lin et al. 2014 no 2) and considered a better representation of bolus clearance by peristalsis (i.e., the bolus tail), as originally described (Dodds et al. 1972, Kahrilas et al. 1988).

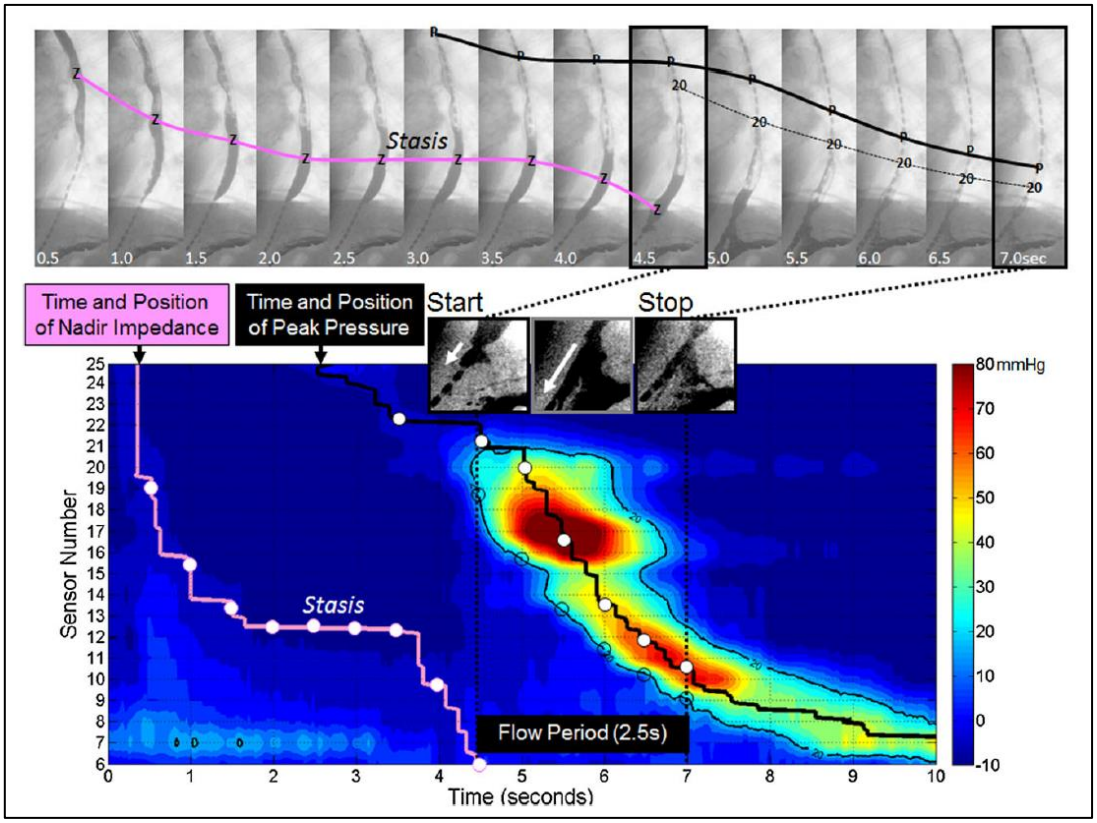


Figure 4.9 Assessment of OGJ bolus flow using pressure-flow analysis when comparing the mean ratio for impedance at peak distension to that at peak contraction (impedance ratio – IR) to radiological bolus transit. (Omari et al 2015 – figure used with permission from publisher).

Lin and colleagues (Lin et al. 2014 no 2) also developed a method of assessing bolus flow through the esophago-gastric junction using similar principles of pressure-flow. The added complexity at the OGJ being crural diaphragm contractions, which periodically halt bolus flow when they exceed the pressure differential between the distal oesophagus and stomach. In short, their method predicts bolus flow across the OGJ when two conditions are met; 1) bolus is present above the OGJ and 2) there pressure gradient permissive of bolus flow. This generates two additional metrics which inform us about bolus flow at the OGJ: bolus presence time (BPT in seconds) and bolus flow time (BFT in seconds). BFT can be used in conjunction with IR to draw conclusions on bolus flow to, and through, OGJ.

4.4.2 Mucosal Integrity

Mucosal inflammatory conditions such as reflux oesophagitis or eosinophilic oesophagitis change mucosal permeability. Mucosal permeability, in turn, alters electrical conductivity of the esophageal wall, due to increased transmucosal movement of electrolytes impacting on impedance measurements (Orlando et al. 2010, Kandulsky & Malfertheiner 2011). Altered mucosal impedance measurements have has been demonstrated in reflux disease and eosinophilic oesophagitis, using pH-MII (Mei & Babaei 2018) and HRMI (Myers & Omari 2014) catheters as well as endoscopically directed devices (Weijenborg et al. 2016, Patel et al. 2019).

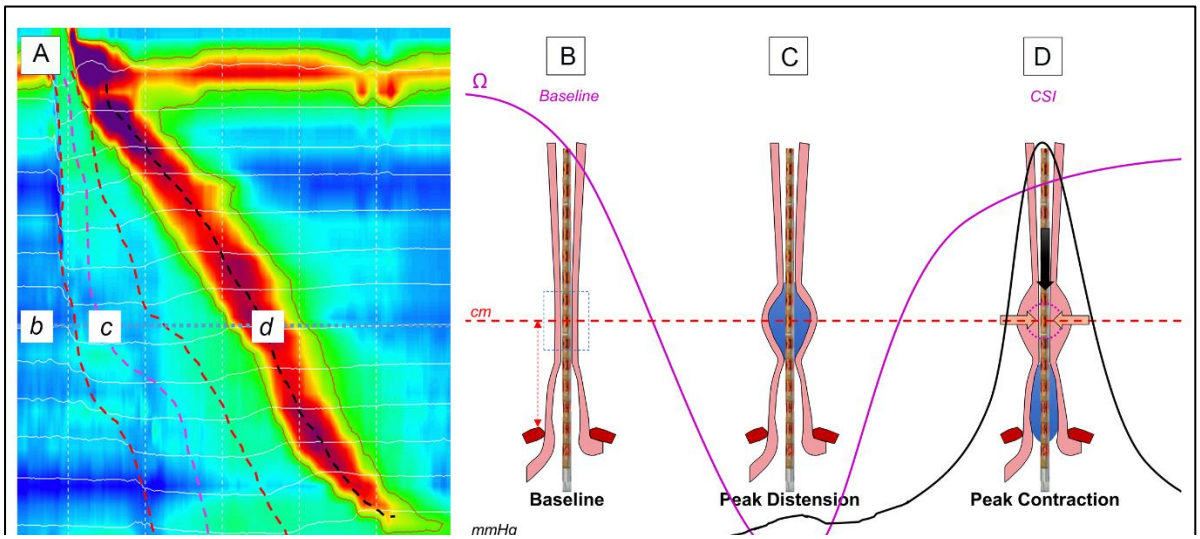


Figure 4.10 Contractile segment impedance (CSI). Figure 4A shows oesophageal pressure topography. The luminal state at each point along the blue dotted line for b,c and d is displayed in the accompanying figures 4B, C and D. Impedance (indigo) and pressure (black) is overlayed. Fig 4B represents the baseline, 4C maximal luminal distension (accompanied by nadir impedance – see text) and 4D represents the impedance measured at the peak of the contraction – contractile segment impedance, which is representative of measured mucosal impedance, which reflects mucosal integrity through measured conductivity. (Own)

During lumen-occlusive oesophageal contractions, the mucosa comes into direct contact with an intraluminal object such as a measurement catheter. If there is a thin film of conductive bolus and a peak pressure exceeding 30mmHg (Kahrilas et al. 1988); impedance measured at the point of maximal contraction, contractile segment impedance (CSI), reflects mucosal, as opposed to intraluminal, impedance (Figure 4.4.3).

Mucosal integrity has also been shown to be reduced in patients with eosinophilic oesophagitis (Choksi et al. 2017). It is important to acknowledge that for impedance-based measurements such as CSI, that these are very specific to the manometry system used, likely related to technical differences in the recording of impedance measurements. Furthermore, when a large residual volume of bolus is present (i.e., when transit fails), this lowers the impedance readings in different oesophageal segments rendering the measurements unreliable for assessing mucosal integrity. To account for this a 30mmHg minimum contraction threshold is applied and the CSI reading is be considered uninterpretable when pressures are lower.

4.5. Radiological Outcomes

4.5.1 Swallowing Safety: PAS Scale

Swallowing safety has been shown to be impaired in ageing (Molfenter et al.2018, Jardine et al. 2018). Rosenbek's penetration and aspiration scale (PAS) (see Table 4.3); describing airway soiling, its extent and whether bolus is cleared from the airway, is universally accepted as the gold standard for the radiological description of penetration/aspiration (Rosenbek et al. 1996).There are difficulties in considering the scale linear (which it clearly is not) or even ordinally when sequential numbers do not reflect the pathophysiology of failed airway protection (Steele & Grace-Martin 2017). An in-depth technical discussion is beyond the scope of this thesis, but the Rosenbek scale is included below along with a proposed re-organization into levels A-D proposed by Steele & Grace-Martin (Steel & Grace-Martin 2017).

Table 4.3 Rosenbek penetration and aspiration scale (PAS)			
Score	Description	Steele & Grace-Martin Level	General Use
1	No penetration/aspiration	A	Normal
2	Superficial penetration and ejected	A	Normal
3	Penetration above vocal folds, not ejected	B	Penetration
4	Penetration contacts vocal folds and ejected	A	Penetration
5	Penetration to vocal fold not ejected	B	Penetration
6	Aspiration below folds but ejected	B	Aspiration
7	Aspiration below vocal fold effort to eject failed	C	Aspiration
8	Aspiration below vocal folds with no effort to eject (silent aspiration)	D	Aspiration

4.5.2 Pharyngeal Residue: Normalized Residue Ratio Scale

The *Normalized Residue Ratio Scale (NRRS*) is a method of objectively assessing radiological residue using computer-based image analysis. Some of the main advantages are its objective nature, reproducibility, and the fact that it can be performed by non-experts, provided they closely follow the methods as described (Pearson et al. 2013).

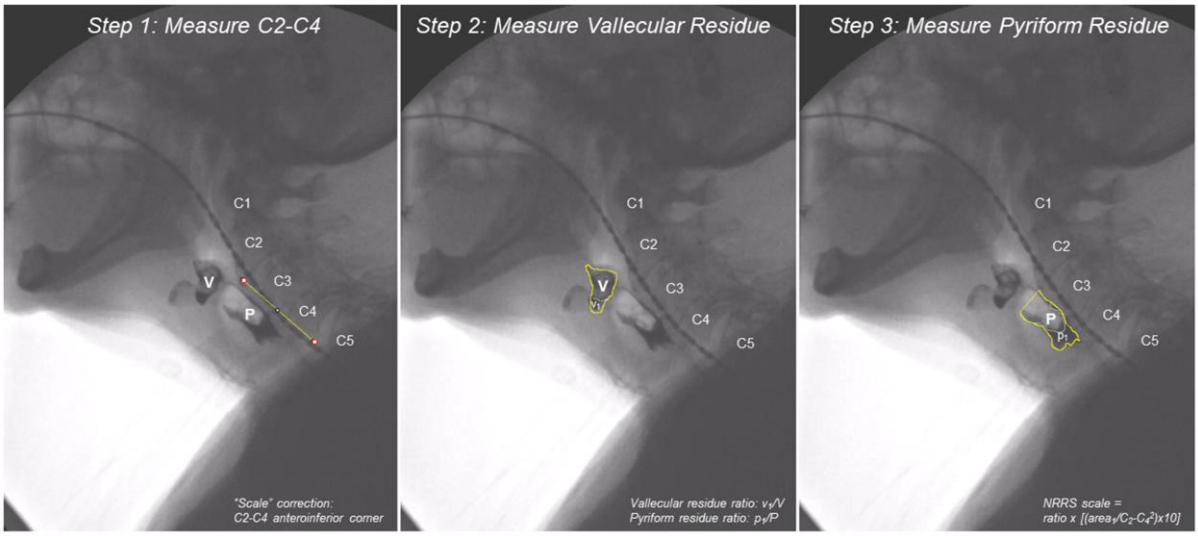


Figure 4.11 Calculation of the Normalized Residue Ratio Scale (NRRS). The first image following return of the larynx to its resting position is exported. A normalization scalar (C_2-C_4 anteroinferior corner) is measured. The ratio of vallecular (V) residue to complete vallecular space (v_1/V); as well pyriform (p_1/P) is calculated. NRRSv (vallecular) and NRRSp (pyriform) residue ratio scales are calculated using a formula, which includes scalar correction. (Own)

Calculation of the NRRS is described in Figure 4.11. In the study described in Chapter 9, measurements were undertaken on exported images for the correctional scale (Fig. 4.11 Step 1), residue for the vallecula (Fig. 4.11 Step 2) and pyriform sinuses (Fig. 4.11 Step 3). The NRRS was calculated according to the formula (valleculae used as example): NRRSv = (v1/V) x [(v1/C2-C42)x10)].

Stokely et al (Stokely et al. 2015) described the residue in 143 normal swallows as ranging between 0 and 0.02 for vallecular residue and 0 for pyriform residue. They also described 95% confidence intervals for abnormal swallows with the lower bounds being 0.1 for 65 swallows with vallecular and 55 swallows with pyriform residue.

4.6 Statistical Analyses

Statistical analyses were carried out using Graphpad Prism (Graphpad Software, San Diego, Ca), Sigmaplot (Systat, San Jose, Ca) and SPSS (IBM, Armonk, NY), and the principles used for analyses are described here.

Unless otherwise specified, metric data were averaged across all single swallows per volume and consistency per subject. For example, a subject who swallowed five x 10ml liquid (ISSDI = 0) boluses, of which one of the boluses was swallowed piecemeal, and therefore excluded, the measurements were reported as the average value of n=4 swallows.

Prior to further analyses data were assessed for normal distribution using the D'Agostino-Pearson normality test. Normally distributed data were subsequently analysed using parametric analyses and non-normally distributed data using non-parametric analyses. For multiple groups an ANOVA with post-test Holm-Sidak (parametric) or Kruskal Wallis test with post-test Dunns (non-parametric) with Bonferroni corrections were used. For repeated measures test the RM-ANOVA or pairwise t-tests (two groups) were used. For comparison between groups a non-paired t-test (parametric) or Mann Whitney test were used. The exception to this were studies (e.g., Chapter 8) where subjects were compared

to their own baseline data and therefore pairwise comparisons were used. For comparing proportions chi-square of Fisher's exact tests were used. Correlations were done using Pearson's (linear) or Spearman (non-linear) correlations.

For some studies more complex statistical modelling were performed, for example repeated measures two-way ANOVA, again with post-hoc tests, or a mixed-model linear regression. These statistical analyses are described in the relevant Chapters. For all statistical tests a p-value of < 0.05 was regarded as indicating statistical significance.

4.7 Addendum: The International Dysphagia Diet Standardization Initiative (IDDSI)

The International Dysphagia Diet Standardization Initiative (IDDSI) is defined as eight levels (0-7) of consistency with drinks measured as levels 0-4 and food levels 3-7 (note overlap for levels 3 and 4). There is detailed description of levels available at:

https://iddsi.org/IDDSI/media/images/Complete_IDDSI_Framework_Final_31July2019.pdf.

The intent of this schema is consistency in application of drink and food consistencies during testing (such as using video fluoroscopy) and during meal. The rheological behaviours of such drinks and food are described as how quickly they drain from a standard syringe, and whether they flow freely from a spoon or fork, or can be eaten using such instruments.

The" food" category (IDDSI level 7) consists of "normal everyday foods of various textures" which can be either hard and crunchy or naturally soft. The "final consistency" is defined as food that can be chewed into a soft, cohesive, and "swallow ready" food bolus. Food can exceed 1.5cm pieces. No measured viscosity defines the food categories.

https://iddsi.org/framework

Part II

Part II: Asymptomatic Older Persons

Chapter 5 Biomechanics of pharyngeal and upper oesophageal sphincter function across the age-range (pharyngo-UOS biomechanics in older persons)

This Chapter includes a re-analysis of recordings used in a previous publication (Omari 2014 – see appendix A) as well newly acquired recordings performed during the course of this PhD.

5.1 Introduction

Oropharyngeal dysphagia (OPD) is prevalent in older people in nursing homes and hospitals, but also in community-dwelling older people (see Chapter 2.2). The presence of OPD places the individual at increased risk of adverse health outcomes such as malnutrition, aspiration pneumonia and death (Serra-Prat et al. 2012). OPD can be detected by subjective or objective means, however, neither give us information on the pathophysiology or biomechanical changes underpinning OPD.

Although reduced upper oesophageal sphincter (UOS) relaxation and opening in healthy older volunteers has been demonstrated, as compared to young, using “pressure only” manometry (Nativ-Zeltzer et al. 2016), the functional consequences of such reduced relaxation can only be demonstrated using “pressure-flow” techniques that inform us about bolus flow through the pharynx and pharyngo-oesophageal segment.

The study by Nativ-Zeltzer (Nativ-Zeltzer et al. 2016) studied a small number of individuals in two “age-brackets”, namely those aged 21 to 40 years of age; and those aged 60-80 years of age. Based on the concept that changes in body systems occur gradually across the lifespan, this study thus may not adequately assess gradual changes in swallowing function across the lifespan, and most importantly, does not include the oldest old (over eighty years of age), where one may expect the most profound changes in swallowing biomechanics to occur.

The aims of this study were to:

1. Assess changes in swallowing biomechanics in the pharynx and at the UOS in different age cohorts ranging from 20 years to those over 80 years of age.
2. Establish a set of “normative values” using standardized bolus volume and viscosity across the age range for studies analysed using swallowgateway.com.

5.2 Methods

5.2.1 Population

Healthy, community-dwelling (i.e., individuals who live in their own home – not institutionalised), volunteers were recruited using community advertising for a study of swallowing using high-resolution impedance manometry. Individual participants were recruited in the age-brackets of 20-39 years of age (yrs), 40-59 yrs, 60-80 yrs, and ≥ 80 yrs, with the purpose of recruiting 15-20 participants per age bracket. Ethics approval was obtained (Southern Adelaide Human Research Ethics Committee no 10.403 & 14.444). Volunteers were reimbursed for travel and out of pocket expenses.

5.2.2 Study procedure

Studies were undertaken as per standard laboratory practice as described in methods (Chapter 4, page 106).

For this study, patients were studied using 5,10ml liquid (IDDSI = 0) and viscous boluses for the initial study (10.403), adding 20ml boluses, if tolerated, for the subsequent studies (14.444).

5.2.3 Data analysis

Manometry data were exported from MMS as American Standard Code for Information Interchange (ASCII) files and imported for further analysis into swallowgateway.com. The technical details of the analysis are described further in Chapter 4 (p. 108), but in short, the metrics derived for the pharynx and UOS are those included in the consensus document from 2019 (Omari et al. 2019), included in Figure. 4.2 and Table 4.1 (Ch. 4, p 108,110).

5.2.4 Statistical Analysis

Descriptive statistics were calculated for each metric per age group (20-39 yrs, 40-59 yrs, 60-80 yrs, ≥ 80 years of age). Data were further analysed as per the methods (Chapter 4, page 90) with the following additional analyses. Three-way ANOVAs for age groups, bolus volume and bolus consistencies were undertaken. Two-way ANOVAs for age groups and gender were undertaken. Correlation for metrics with age were calculated using Pearson correlations. A P-value of < 0.05 was considered statistically significant.

5.3 Results

5.3.1 Study population

Demographics for the study population are included as Table 5.1

Table 5.1 Study population

	Group 1 (20-39 yrs)	Group 2 (40-59 yrs)	Group 3 (60-79 yrs)	Group 4 (≥ 80 yrs)
Number (n)	20	20	25	25
Age (mean±sd)	28±7	53±7	70±6	86±4
M:F	7:13	6:14	10:15	15:10

5.3.2 Pharyngo-UOS Pressure-flow Metrics

Results for liquids are included for pharyngeal and UOS pressure-flow variables in Table 5.4. Median values across the age groups are shown for pharyngeal contractility (Figure 5.1) and UOS IRP (Figure 5.2), with both showing an upward trend with increasing age to age 80, but with pharyngeal contractility reducing again beyond 80 years of age. Upper oesophageal sphincter maximum admittance, a correlate of opening diameter, is shown to reduce with age up to the 60-79 yrs band and then remained static without further decline. (Figure 5.3). Similar findings were demonstrated for viscous swallowing (not shown).

Normative values for both 5ml and 10ml liquid volumes are shown per age group in Table 5.4 (arrows show the directionality of abnormal values). Liquid normative values (5ml) for the entire 20-59 yrs age cohort are shown in Table 5.6, while results for 5 and 10ml viscous boluses are included in Tables 5.7 & 5.8.

5.3.3 Group, Volume and Viscosity Effects

The results for three-way ANOVA with group, volume and consistency as factors are included as Table 5.2

Table 5.2 Three-way ANOVA with factors Group (Age), Volume, and Viscosity (Consistency)

	Groups (Age)		Volume		Consistency		Other
	F	P-value	F	P-value	F	P-value	
PhCI	↑**14,408**	**<0.001**	2.035	0.15	1.184	0.277	Nil
VCI	2.007	0.11	0.056	0.81	1.343	0.25	Nil
MCI	↑**6.340**	**<0.001**	3.084	0.08	0.447	0.50	Nil
HCI	↑**11.446**	**<0.001**	0.382	0.54	0.016	0.90	Nil
IBP	↑**6.739**	**<0.001**	↑**6.593**	**0.01**	0.698	0.40	Nil
UOS IRP	↑**16.891**	**<0.001**	1.073	0.30	↑**19.329**	**<0.001**	Nil
UOS RT	↑**14.338**	**<0.001**	0.245	0.62	↓**7.300**	**0.007**	Nil
UOS Max Ad	↓**19.764**	**<0.001**	↑**25.558**	**<0.001**	↓**163.243**	**<0.001**	Yes*
Group effects for UOS Max Ad – Group x Volume (F=3.622; P=0.01); Group x Consistency (F=7.070; P=0.008)							
Average of five swallows per individual							

There were significant main effects for *all* pharyngeal contractility and UOS metrics between groups (P < 0.001), with the exception of the velopharyngeal contractile integral. Volume and viscosity effects only occurred for UOS metrics, summarized in Table 5.3 (values for all age groups combined shown).

Table 5.3 Volume, and Viscosity Results (All Groups)

	Liquids		Viscous	
	5ml	10ml	5ml	10ml
IBP (mmHg)	10.3±1.2	13.6±1.5*	10.4±1.4	16.1±1.7***
UOS IRP (mmHg)	0.8±0.9	1.9±1.0	4.3±1.1	8.4±1.4*
UOS RT (sec)	0.565±0.01	0.577±0.01	0.537±0.01	0.547±0.01
UOS Max Ad (mS)	5.7±0.2	6.9±0.3**	4.0±0.1	4.3±0.1
Average of five swallows per individual				

Table 5.4 Group Results for Liquids (IDDSI level 0)

	Group 1 (20-40 yrs)[a]		Group 2 (40-59 yrs)[b]		Group 3 (60-79 yrs)[c]		Group 4 (≥ 80 yrs)[d]	
	5ml	10ml	5ml	10ml	5ml	10ml	5ml	10ml
PhCI (mmHg.s.cm)	250±28[ccc]	282±33[c]	366±38	419±83	459±41[aaa]	457±41[a]	342±36	341±42
VCI (mmHg.s.cm)	57±10	70±12	94±16	76±12	84±18	81±13	85±9	83±13
MCI (mmHg.s.cm)	128±13	141±17	166±21	215±38	170±18	166±16	136±14	138±15
HCI (mmHg.s.cm)	58±9[ccc]	64±12[cc]	97±13	111±32	141±18[aaa]	131±17[aa]	110±16	98±13
IBP (mmHg)	9.4±1.9	10.36.±1.8	6.4±1.6	10.0±5.6	9.0±1.9	14.1±1.6	15.4±3.2	16.1±3.3
UOS IRP (mmHg)	-2.6±1.6[dd]	-2.0±2.0[cc,dd]	-1.7±1.9[d]	-5.8±3.1	0.4±1.4	1.5±1.4[aa]	5.9±1.8[aa,b]	7.0±1.8[aa]
UOS RT (sec)	0.530±0.022[bbb]	0.535±0.028	0.685±0.019[a,c,d]	0.649±0.031	0.546±0.021[bb]	0.569±0.022	0.556±0.016[bb]	0.549±0.019
UOS Max Ad (mS)	7.1±0.4[ccc,ddd]	8.2±0.7[c,d]	6.5±0.4[d]	8.3±1.3	5.0±0.3[aaa]	6.2±0.4[a]	4.9±0.2[aaa,b]	6.3±0.3[a]

Between group comparison with: Group 1 a = P < 0.05, aa = P < 0.01, and aaa = P < 0.001; Group 2 b = P < 0.05, bb = P < 0.01, and bbb = P < 0.001; Group 3 c = P < 0.05, cc = P < 0.01, and ccc = P < 0.001; Group 4 d = P < 0.05, dd = P < 0.01, and ddd = P < 0.001.
Average of five swallows per individual

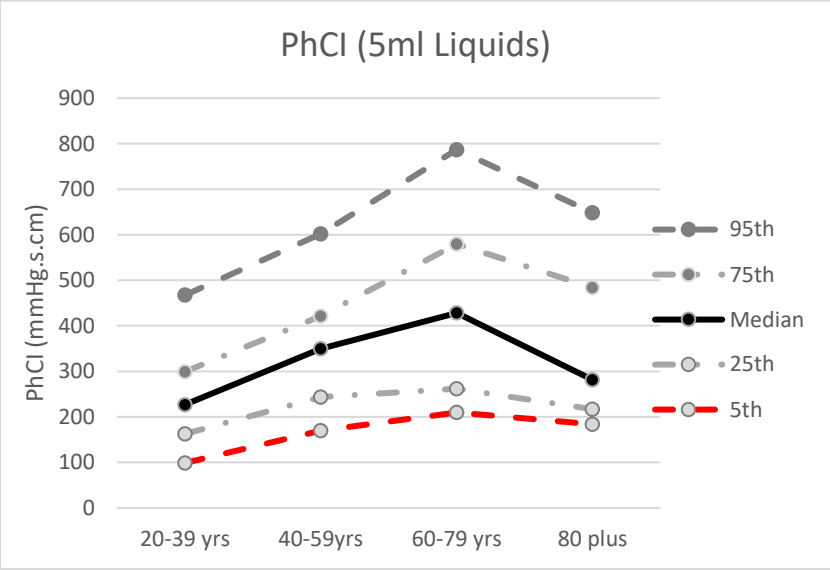


Fig 5.1 Pharyngeal contractile integral – PhCI, a measure of overall pharyngeal contractility, for 5ml liquids in different ages.

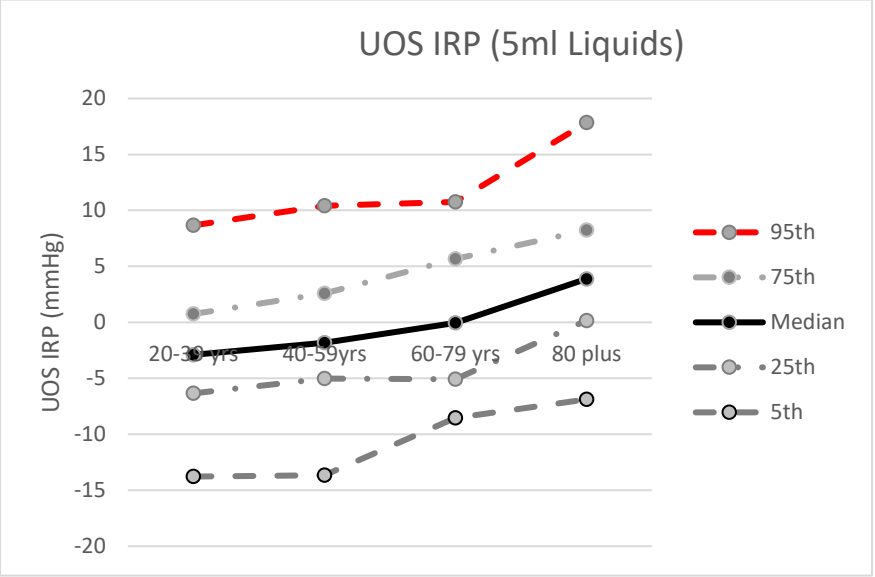


Fig 5.2 Upper oesophageal sphincter integrated relaxation pressure - UOS IRP, a measure of UOS relaxation, for 5ml liquids in different ages.

Table 5.5 Cutoffs for Liquids Normative Values (5th/95th percentile)

	Group 1 (20-40 yrs)		Group 2 (40-59 yrs)		Group 3 (60-79 yrs)		Group 4 (≥ 80 yrs)	
	5ml	10ml	5ml	10ml	5ml	10ml	5ml	10ml
PhCI (mmHg.s.cm)	↓86	↓155	↓170	↓175	↓197	↓199	↓**115**	↓113
VCI (mmHg.s.cm)	↓13	↓11	↓42	↓38	↓12	↓15	↓**18**	↓30
MCI (mmHg.s.cm)	↓51	↓68	↓79	↓96	↓47	↓42	↓**33**	↓30
HCI (mmHg.s.cm)	↓9	↓17	↓25	↓27	↓50	↓67	↓**26**	↓23
IBP (mmHg)	↑25	↑26	↑18	↑45	↑25	↑32	↑**61**	↑65
UOS IRP (mmHg)	↑14	↑15.3	↑14	↑14	↑12	↑15.9	↑**32**	↑34
UOS RT (sec)	↓0.348	↓0.308	↓0.522	↓0.556	↓0.374	↓0.390	↓**0.425**	↓0.404
UOS Max Ad (mS)	↓4.0	↓4.5	↓3.1	↓3.3	↓3.4	↓3.9	↓**3.2**	↓3.4
Average of five swallows per individual								

Table 5.6 Normative values for 5ml Liquids (IDDSI level 0) for 20-59 yrs

	Mean ±SEM	Median [25thP;75thP]	5th P	95th P
PhCI (mmHg.s.cm)	308±25	283[179;417]	**101**	548
VCI (mmHg.s.cm)	75±10	53[43;84]	**26**	225
MCI (mmHg.s.cm)	147±12	127[92;181]	**62**	307
HCI (mmHg.s.cm)	78±8	69[35;100]	**12**	171
IBP (mmHg)	7.9±1.2	5.4[3.1;15.4]	-4.7	**24**
UOS IRP (mmHg)	-2.1±1.2	-2.2[-6.1;2.2]	-17.2	**14.4**
UOS RT (sec)	0.608±0.019	0.612[0.520;0.717]	**0.351**	0.781
UOS Max Ad (mS)	6.8±0.3	6.5[5.2;8.3]	**3.2**	10.1
Average of five swallows per individual				

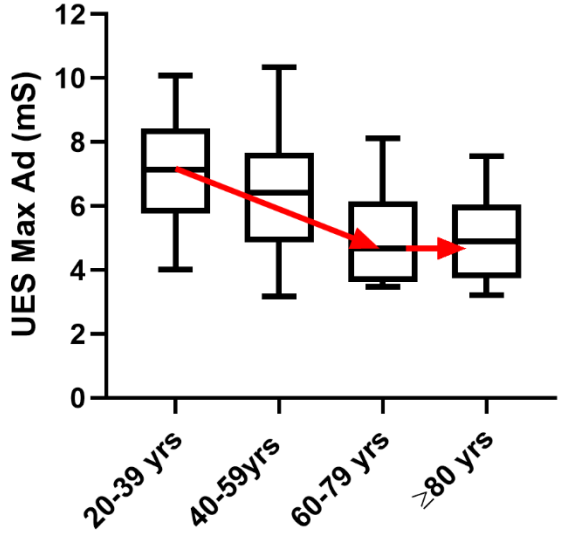


Fig 5.3 Upper oesophageal sphincter maximum admittance – UOS Max Ad, a measure of UOS cross sectional area, for 5ml liquids in different ages.

Table 5.7 Group Results for Viscous (IDDSI level 4)

	Group 1 (20-40 yrs)		Group 2 (40-59 yrs)		Group 3 (60-79 yrs)		Group 4 (≥ 80 yrs)	
	5ml	10ml	5ml	10ml	5ml	10ml	5ml	10ml
PhCI (mmHg.s.cm)	231±21[cc]	275±30[c]	330±33	414±84	407±37[aa]	419±36[a]	314±32	339±33
VCI (mmHg.s.cm)	52±8	62±10	75±9	78±19	74±12	82±15	69±8	73±7
MCI (mmHg.s.cm)	115±10	136±15	157±16	193±33	162±19	172±20	129±14	141±15
HCI (mmHg.s.cm)	61±8[cc,d]	76±15[c]	90±14	122±33	119±15[aa]	123±16[a]	109±14[a]	102±11
IBP (mmHg)	9.4±2.7	12.4±3.0	4.6±1.6	13.2±4.1	9.6±1.9	14±1.4	17.1±3.5	20.8±4
UOS IRP (mmHg)	1.9±2.1	4.8±3.2	-0.7±2.2[dd]	0.5±4.0	6.1±2.0	8.2±1.5	8.8±1.9[bb]	12.9±2.9
UOS RT (sec)	0.526±0.022[b]	0.523±0.026	0.606±0.018[a,cc,dd]	0.607±0.028	0.505±0.018[bb]	0.537±0.018	0.526±0.013[bb]	0.550±0.020
UOS Max Ad (mS)	4.4±0.2[dd]	4.8±0.3	4.3±0.2[dd]	5.1±0.3	3.9±0.2	4.2±0.3	3.5±0.1[aa,bb]	3.9±0.1
Average of five swallows per individual								

Table 5.8 Cutoffs for Viscous Normative Values (5th/95th percentile)

	Group 1 (20-40 yrs)		Group 2 (40-59 yrs)		Group 3 (60-79 yrs)		Group 4 (≥ 80 yrs)	
	5ml	10ml	5ml	10ml	5ml	10ml	5ml	10ml
PhCI (mmHg.s.cm)	97	152	181	272	165	145	132	125
VCI (mmHg.s.cm)	3	17	25	44	0	7	15	20
MCI (mmHg.s.cm)	57	69	88	105	44	35	37	33
HCI (mmHg.s.cm)	15	18	46	66	36	52	32	33
IBP (mmHg)	41	35	14	36	26	24	61	77
UOS IRP (mmHg)	19	27	13	13	26	23	32	56
UOS RT (sec)	0.296	0.292	0.472	0.510	0.350	0.407	0.392	0.391
UOS Max Ad (mS)	3.3	3.4	3.0	4.2	2.3	2.5	2.2	2.8
Average of five swallows per individual								

5.3.4 Gender effects

The results for two-way ANOVA with factors group and gender are included (Table 5.9)

Table 5.9Two-way ANOVA with factors Group (Age) and Gender

	Groups (Age)		Gender		Group x Gender	
PhCI	**19.383**	**<0.001**	**14.753**	**<0.001**	**4.992**	**0.002**
VCI	2.221	0.09	**6.610**	**0.01**	**10.917**	**<0.001**
MCI	**7.748**	**<0.001**	**9.055**	**0.003**	2.279	0.08
HCI	**14.438**	**<0.001**	**14.083**	**<0.001**	**3.166**	**0.03**
IBP	**5.129**	**0.002**	2.705	0.10	2.223	0.09
UOS IRP	**12.262**	**<0.001**	1.937	0.17	**3.015**	**0.03**
UOS RT	**11.500**	**<0.001**	0.026	0.87	**12.987**	**<0.001**
UOS Max Ad	**8.839**	**<0.001**	1.521	0.22	**2.940**	**0.03**
Average of five swallows per individual						

PhCI was higher for males as compared to females in the two oldest age groups (60 to 79 yrs: M 539±26 vs. F 366±21mmHg.s.cm; P < 0.001) and (≥80 yrs: M 371±20 vs. F 260±29mmHg; P = 0.002). VCI was higher for males in the three younger age groups (P < 0.05); MCI and HCI was higher for males in the two oldest groups (P < 0.01)

UOS relaxation as measured through UOS IRP was reduced only in the oldest (≥ 80 yrs) males, (M 10.9±1.1 vs. F 3.7±1.6; P < 0.001). UOS relaxation duration was longer in males in the younger ages (P < 0.05), but shorter over eighty years of age (P < 0.05). UOS maximum admittance was the least in the oldest males (P = 0.004)

5.3.5 Correlations of Age with Pharyngeal and UOS Metrics

Age was correlated with all current pharyngeal and UOS metrics, including those currently still under review. Data are shown for the currently accepted metrics (Table 5.10).

Table 5.10 Correlations of Age with Pharyngeal and UOS Metrics.

	5ml L	10ml L	5ml V	10ml V
PhCI (mmHg.s.cm)	**0.216**	0.119	**0.214**	0.119
VCI (mmHg.s.cm)	0.134	0.069	0.120	0.0814
MCI (mmHg.s.cm)	0.012	-0.067	0.049	-0.026
HCI (mmHg.s.cm)	**0.294**	0.194	**0.274**	0.149
IBP (mmHg)	0.199	0.166	0.174	0.178
			0	
UOS IRP (mmHg)	**0.373**	**0.393**	**0.310**	**0.277**
UOS RT (sec)	-0.012	-0.015	-0.093	0.050
UOS Max Ad (mS)	**-0.482**	**-0.402**	**-0.406**	**-0.376**
Bold values indicate significant P-value: P < 0.05 *Average of five swallows per individual*				

Age correlated with reduced UOS relaxation, reduced extent of UOS opening cross sectional area and an increase in hypopharyngeal contractility.

Age also correlated with increased mean hypopharyngeal peak pressures (r = 0.215; P 0.04) and *reduced* proximal oesophageal contractility (r = -0.256; P = 0.01). Age showed no other correlations for any pharyngeal metrics currently calculated by swallowgateway.com.

5.4. Discussion

This study provides novel insights into the pharyngo-UOS pressure-flow metrics in older persons. There was a gradual reduction in the extent of UOS relaxation and opening, as measured using UOS IRP and maximum admittance, across the lifespan (Figures 5.4 & 5.5). Hypopharyngeal contractility increased into the eighth decade of life, after which it slightly reduced. This combination of reduced UOS relaxation and increased hypopharyngeal contractility had previously been demonstrated (Kern et al. 1999, Nativ-Zeltzer et al. 2016). However, our study also showed evidence of reduced UOS cross-sectional area and that the increased hypopharyngeal contractility may reach a ceiling beyond which no further measured increase occurred. These data suggest there is potentially a limit of compensation in

overcoming flow resistance at the UOS and the reduction in hypopharyngeal contractility in late life (over eighty years of age) may represent a failure in compensatory mechanisms.

The compensatory mechanisms employed by healthy older persons during normal eating behavior such as reducing bite sizes (volume) or changes in consistencies have not been fully described. I postulate that such swallowing behaviour may be a compensatory mechanism for upper oesophageal sphincter dysfunction, described in this study and also by others (Kern et al. 1999, Nativ-Zeltzer et al. 2016). Biomechanically there is a limited extent to which the UOS can accommodate boluses. When the upper limit is exceeded, airway penetration or residue with coughing or choking episodes may occur. This upper “dysphagia” limit had been described by some as occurring at 20ml for liquid boluses (Ertekin et al 1996, Aydogdu et al. 2015). Increased propulsion by the posterior tongue may increase pressure generation within the pharyngeal chamber as a further compensatory mechanism, but we know that tongue strength decreases in later life (Fei et al. 2013, Liu et al. 2021, Chen et al. 2021). The data presented here suggest that UOS dysfunction is the predominant pharyngeal-UOS pathophysiology in healthy ageing, rather than the ongoing or progressive decline in function proposed by Fried (Fried et al. 2001), or the accumulation of deficits, as proposed by Rockwood and colleagues (Rockwood & Mitnitski 2007, Rockwood & Mitnitski 2011, Rockwood & Howlett 2019). Specifically, what we see is that dysfunction in one component of the swallowing system is compensated for by other parts, until such time that this compensatory mechanism is no longer able to overcome the deficit or fails itself. As a consequence, there is potentially a sharp decline in swallowing function in later life due to what we can call compensatory failure. This study suggests that there is a volume threshold for failure of safe pharyngo-UOS swallowing. Per volume safe swallowing threshold may be breached as a result of progressive pharyngeal weakness in advanced old age, or temporarily during intercurrent illnesses.

The 5ml and 10ml boluses used in this experiment did not breach the safety threshold for aspiration, however, larger bolus volumes may do so. The “Dysphagia limit” concept, which denotes the largest bolus volume that can be swallowed in a single swallow (Ertekin et al. 1996, Aydogdu et al. 2015)., The volumes used in this experiment may not have been sufficient to test the limit of swallowing function. Furthermore, I was fastidious in excluding multiple swallows from the analysis, as the smaller bolus swallowed would falsely decrease the extent of UOS opening. It would be of interest to look at multiple swallowing behavior, swallowing of larger boluses and sequential swallowing behavior.

In summary, this study of swallowing function and dysfunction in ageing showed evidence of UOS dysfunction in the oldest cohort. A reducing extent of UOS opening is compensated for by increasing hypopharyngeal contractility. Once advanced old age is reached, compensatory mechanisms fail, and at the same time UOS relaxation reduces.

The aged swallow can still accommodate smaller bolus volumes safely. We also do not yet understand whether there are “downstream” consequences, such as reduced triggering of oesophageal peristalsis. It is also critical to evaluate whether targeting the UOS for therapeutic interventions in age related dysphagia, or in a prophylactic context, has merit for delaying age-related decline in swallowing function.

Chapter 6 Impaired bolus clearance in asymptomatic older adults during high-resolution impedance manometry

As published

Abstract

Background Dysphagia becomes more common in old age. We performed high-resolution impedance manometry (HRIM) in asymptomatic healthy adults (including an older cohort >80 years) to assess HRIM findings in relation to bolus clearance.

Methods Esophageal HRIM was performed in a sitting posture in 45 healthy volunteers (n = 30 young control, mean age 37 ± 11 years and n = 15 older subjects aged 85 ± 4 years) using a 3.2-mm solid-state catheter (Solar GI system; MMS, Enschede, The Netherlands) with 25 pressure (1-cm spacing) and 12 impedance segments (2-cm intervals). Five swallows each of 5- and 10-mL liquid and viscous bolus were performed and analysed using esophageal pressure topography metrics and Chicago classification criteria as well as pressure-flow parameters. Bolus transit was determined using standard impedance criteria. A p-value <0.05 was considered significant.

Key Results Impaired bolus clearance occurred more frequently in asymptomatic older subjects compared with young controls (YC) during liquid (40 vs 18%, v2 = 4.935; $p < 0.05$) and viscous (60 vs 17%; v2 = 39.08; $p < 0.001$) swallowing. Longer peristaltic breaks ($p < 0.05$) and more rapid peristalsis (L: $p < 0.004$, V: $p = 0.003$) occurred in the older cohort, with reduced impedance-based clearance for both bolus consistencies (L: $p < 0.05$, V: $p < 0.001$). Decreased peristaltic vigour (distal contractile integral <450 mmHg/s/cm) was associated with reduced liquid clearance in both age groups ($p < 0.001$) and of viscous swallows in the older group ($p < 0.001$). Impedance ratio, a marker of bolus retention, was increased in older subjects during liquid ($p = 0.002$) and viscous ($p < 0.001$) swallowing

Conclusions & Inferences Impaired liquid and viscous bolus clearance, esophageal pressure topography, and pressure-flow changes were seen in asymptomatic older subjects.

6.1 Introduction

Dysphagia is common in older individuals[1], particularly in extreme older age[2-4]. With a rapidly aging population in most developed countries, dysphagia will become an increasing clinical problem. Although swallowing and eating disorders are particularly common in hospital and nursing home settings[1,5], community dwelling individuals are also affected[4]. Aged dysphagia is multifactorial, with edentulousness, salivary changes, neuromuscular disease(s), diabetes mellitus, Sjogren's syndrome, tumours and paraneoplastic phenomena, drugs, surgical interventions, and structural or age-related physiological changes all contributing factors[1]. Many individuals are affected by oropharyngeal dysphagia; however, several causes of esophageal dysphagia occur more commonly in the aged[6,7].Soergel et al. originally described 'presbyesophagus' to occur in those aged over 90 years[2], and being associated with delayed esophageal clearance on radiology (defined as clearance duration in the excess of 20 s)[2]. The consequences of dysphagia in older subjects include social isolation, malnutrition/sarcopenia, and aspiration pneumonia, all of which can lead to a poor prognosis during any intercurrent illness[8].

Although the data are conflicting, previous manometric studies have reported several changes in esophageal motility that are unique to older adults. A study in healthy volunteers aged from 23 to 86 years showed increased esophageal stiffness and reduced peristaltic function (both primary and secondary) with advancing age[9]. Further to this, a pilot study of esophageal clearance including volunteers over 65 years suggested a trend toward impaired liquid and viscous bolus clearance in older men[10]. Previous work by our group demonstrated changes in lower esophageal sphincter (LOS) function in the elderly (over 80 years), in particular incomplete relaxation and reduced basal pressure, although no changes in peristaltic function were observed[11]. In contrast, a recent study by Kawami et al.[12] found that the adequacy of secondary peristalsis was reduced in older age (over 65 years), but the success of primary peristalsis, the distal contractile integral, and LOS pressure were similar between young and older healthy subjects. Interpretation of these results is hampered by varying definitions used to describe the age limit for older cohorts.

Software-based esophageal pressure-flow analysis (PFA) of high-resolution impedance manometry (HRIM) recordings has recently been described in an attempt to understand the correlation between pressure-flow findings and patient symptoms and outcomes[13-18]. Esophageal PFA adds to the traditional use of impedance to track bolus transit (via impedance drop and return to 50% of baseline) by determining maximum luminal cross-sectional area at the nadir impedance[19-21]. This enables the accurate determination of bolus-related pressures and the relationship of these to both distending and contractile forces[21,22]. Recent data by Kim et al. have shown that the inverse of impedance (admittance) linearly correlates with esophageal cross-sectional area measured with intraluminal ultrasound[20], confirming the correlation of nadir impedance with intraluminal bolus presence[19,21]. Furthermore, esophageal PFA has shown symptom correlation in patients with broad dysphagia, post-surgical[15], and non-obstructive[16,17] dysphagia. This analysis may also be a useful adjunct in studying asymptomatic individuals, including the ability to detect subtle abnormalities not obvious using the Chicago classification system[23].

We hypothesized that failed bolus clearance would occur more commonly in asymptomatic older subjects during viscous swallows. The aim of this study was to use intraluminal impedance methods to characterize bolus clearance in the upright posture for both healthy aged and young cohorts. Further aims were to determine the manometric correlates of failed clearance as detected by intraluminal impedance and to perform pressure-flow analyses to detect subtle changes in esophageal propulsive physiology.

6.2 Materials and Methods

6.2.1 Study Participants

Forty-five healthy volunteers (aged 20–93 years, 21 M) were recruited through community advertisement. A screening history was performed in all subjects to exclude (i) past or present swallowing difficulties, (ii) symptoms suggestive of a motility disorder, (iii) upper gastrointestinal conditions including gastroesophageal reflux disease, (iv) diabetes mellitus, (v) previous history of gastrointestinal surgery, and (vi) prescription medications known to

affect gastrointestinal motility. To further exclude underlying dysphagia, all potential subjects performed a previously validated Dakkak questionnaire[24] to assess the esophageal phase of swallowing for different food consistencies. Only subjects with a normal score (Dakkak = 0) were included in the study. Bodyweight and height and current or past smoking details were also recorded. Enrolled subjects were stratified into the following two groups: younger controls and older subjects (>80 years).

The study protocol was approved by the Southern Adelaide Clinical Human Research Ethics Committee (Approval No. 403.10). All participants gave written informed consent prior to enrolment, and studies were performed at the Repatriation General Hospital, Daw Park, South Australia. AIM PFA of the pharynx has previously been reported in this cohort of subjects.4 The esophageal data reported in this study include only individuals where technically satisfactory esophageal tracings were also obtained.

6.2.2 Measurement technique

High-resolution impedance manometry was performed in a sitting posture using a 10 French (3.2 mm diameter) solid-state pressure-impedance assembly. This incorporated 25 pressure sensors (1 cm spacing) and 12 adjacent impedance segments (2 cm in length) (Unisensor Inc, Attikon, Switzerland). Pressure and impedance data were acquired at 20 Hz (Solar GI acquisition system; MMS, Enschede, The Netherlands). In order to obtain esophageal tracings, this catheter was repositioned following pharyngeal recordings in the majority of subjects and the swallowing protocol repeated.

6.2.3 Study protocol

Following nasal administration of co-phenylcaine forte spray and 2% lignocaine gel, subjects were intubated with the sensors in a posterior orientation. The assembly was positioned with the recording segment spanning the esophageal transition zone to proximal stomach. Following a 10 min accommodation period, subjects received five 5- and 10-mL boluses of liquid (0.9% normal saline) and standardized viscous bolus (EFT Viscous Swallow Challenge Medium, viscosity 13 000 cP; Sandhill Scientific, Denver, CO, USA) via a syringe and asked

to swallow once on cue. Studies were performed in a sitting posture with head in a neutral position.

6.2.4 Data analysis: Esophageal pressure topography

Analysis of esophageal pressure topography (EPT) was based on the Chicago Classification Version3.0 diagnostic algorithm and definitions for esophageal manometry[25] using Solar GI HRIM software (Medical Measurement Systems, Utrecht, The Netherlands). For Chicago analysis and bolus clearance, both 5- and 10-mL volumes were analysed; however, only median results for the 5 mL bolus volume are displayed (Tables 1 and 2). Only studies with more than eight complete liquid or viscous swallows were included in the analysis of the Chicago classification and for the assessment bolus clearance. The Chicago parameters of 4s integrated relaxation pressure (IRP4), peristaltic break length/isocontour defect (ICD), contractile front velocity (CFV), distal contractile integral (DCI), and distal latency (DL) were measured. The IRP4 (mmHg) was determined as the lowest maximum LOS pressure measured with an electronic sleeve sensor for four contiguous or non-contiguous seconds in a 10-second period following swallow onset. Chicago classification of esophagogastric junction (EGJ) morphology subtype was also determined[23]. The ICD (cm) was determined as the axial length of defects in the 20 mmHg isobaric contour[26]. Distal contractile integral (mmHg/s/cm) was determined for the distal esophageal segment as amplitude 9 duration 9 length of the contraction in excess of 20 mmHg. The CFV (cm/s) was determined as the slope of the tangent approximating the 30 mmHg isocontour between the proximal transition zone and contractile deceleration point (CDP). The DL (s) was determined as the time from swallow onset (either through upper esophageal sphincter [UES] relaxation or the onset of impedance drop at the most proximal channel) to the CDP[27].

6.2.5 Data analyses: Pressure-flow analysis

Data were exported as comma separated values and esophageal PFA was performed using MATLAB based automated software (Esophageal AIMplot software; T Omari©; The MathWorks Inc, Natick, MA, USA). Five manually assigned observer-determined regions of interest were used to guide analyses[13,18] (see Figure 6.1). Pressure and/or flow metrics were

determined across the LOS and esophageal body distal to the transition zone[10]. These included the following: (i) pressure at nadir impedance (mmHg), (ii) peak pressure (PeakP, mmHg), (iii) intra-bolus pressure (IBP, mmHg), (iv) IBP slope (mmHg/s), (v) time interval from nadir impedance to peak pressure (TNIPP, s), (vi) pressure-flow index (PFI), and (vii) ratio of nadir impedance to impedance at the time of peak pressure (impedance ratio [IR]; Fig. 6.1).

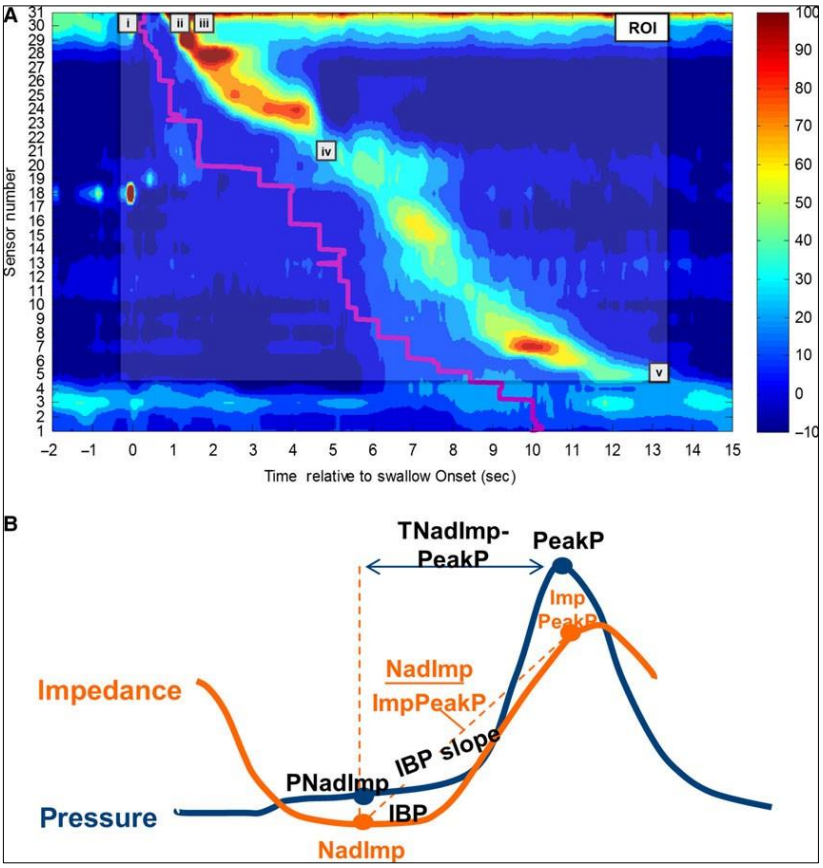


Figure 6.1 (A) Esophageal pressure topography (Clouse) plot of esophageal swallow with nadir impedance (maximal luminal cross-sectional area) in purple. Five regions of interest are selected for the calculation of pressure-flow metrics: (i) swallow onset, (ii) start of peristalsis, (iii) proximal peristaltic wave, (iv) mid transition zone, and (v) proximal margin of LOS high-pressure zone. (B) Multiple variables are calculated using Matlab™ algorithms, including pressure (peak pressure, pressure at nadir impedance, and intrabolus pressure), impedance (nadir impedance and impedance at peak pressure), and timing variables (time from nadir impedance to peak pressure). Variables are combined as a pressure-flow index, relating to bolus perception, and impedance ratio relating to bolus retention (see text).

The TNIPP is indicative of the latency from bolus distension to esophageal contraction. The PFI (previously named dysphagia risk index[15]) was developed in the context of post-fundoplication dysphagia and amplifies differences in key metrics in relation to symptoms. This variable is calculated using the formula PFI = (IBP * IBP slope)/(TNIPP) and is higher in circumstances of greater bolus pressurization in relation to bolus flow[18]. For example, PFI is increased in both post-fundoplication dysphagia[15] and non-obstructive dysphagia[16,17]. Impedance ratio, which is indicative of bolus clearance, was calculated as a marker of incomplete bolus transit. It defines the proportion of the bolus present at the time of peak

esophageal contraction pressure relative to the bolus present at the time of maximal esophageal distension/flow (high ratio = incomplete transit)[17,18,21].

6.2.6 Data analysis: Impedance-based assessment of esophageal bolus transport

Bolus presence time was determined for all impedance segments as the time interval between bolus entry (50% drop from 3-s pre-swallow basal impedance) and bolus exit (recovery to more than 50% of basal value for more than 5 s)[28,29]. Per patient analysis of all liquid and viscous swallows was performed. Bolus clearance was considered normal with ≥80% clearance of liquid and ≥70% with viscous[28.30].

6.2.7 Statistical analysis

Data were analyzed using Sigmaplot 13 (Systat Software Inc., San Jose, CA, USA). Data were assessed for a normal distribution using the D'Agostino & Pearson omnibus test. Pairwise comparisons were done via independent sample t-test or Mann– Whitney U-test when non-normally distributed. Data presented are mean ± SEM or median (IQR). Proportions were compared using Chi-square test. A two-way ANOVA was used to compare per subject category (YCs and older subjects) and per clearance (cleared and non-cleared) with Holm-Sidak pairwise multiple comparison procedure for Chicago and pressure-flow metrics. A p-value of <0.05 was considered statistically significant throughout.

6.3 Results

All subjects tolerated the study procedure well, and no adverse events were reported. Older subjects (n = 15; aged 85 ± 4 years) were significantly older than the younger group (n = 30; aged 37 ± 11 years) ($p < 0.001$).

6.3.1 Analysis of swallows by EPT criteria

The results of Chicago classification analyses are summarized in Table 6.1. There was a longer ICD in older subjects for both liquid ($p = 0.05$) and viscous ($p = 0.03$) swallows, when compared with younger controls. The CFV was higher with both consistencies in the older group (L: $p = 0.004$ and V: $p = 0.003$). Examples of EPT are shown in Fig. 6.2.

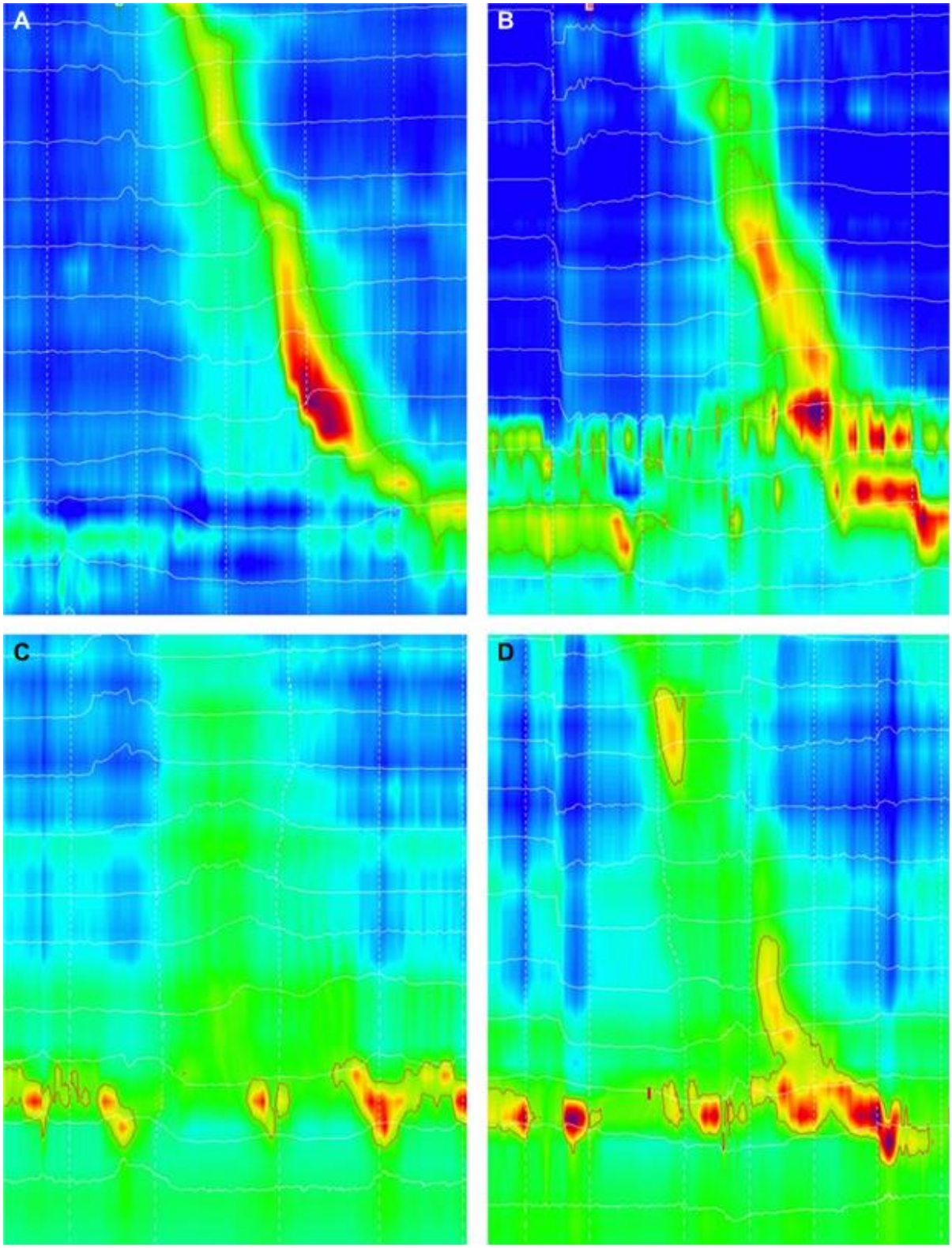


Figure 6.2 Esophageal pressure topography examples of a (A) normal swallow in young control subject with clearance, (B) EGJ obstruction in older subject with clearance,(C)failed swallow in younger subject without clearance (impedance-based), and (D) fragmented peristalsis in older subject without clearance.

Chicago classification of EPT Analysis of studies during liquid swallows showed a higher proportion of failed peristalsis in subjects aged over 80 years (O: 26.7% vs YC: 3.3%; v2 = 5.513; p = 0.02). The remaining studies were an equal proportion of normal studies (O: 46.7% vs YC: 57.9%; p = 0.29) and ineffective esophageal motility (O: 26.7% vs YC: 38.8%; p = 0.64).

Analysis of studies during viscous swallows showed a similar proportion of failed peristalsis (O: 20% vs YC: 7.1%; p = 0.18) and IEM (O: 26.7% vs YC: 20%;p = 0.51) with a trend toward fewer normal studies in older subjects (O: 46.7% vs YC: 73.3%; p = 0.08).

One younger subject (3.3%) had an EGJ morphology subtype III, consistent with a hiatus hernia. The remaining distributions in this group were n = 13 EGJ type I (43.3%) and n = 16 type II (53.3%). In the older group, n = 9 subjects had an EGJ type I (60%) and n = 4 type II (26.6%), but no type III was observed. Two older subjects were unable to be analysed due to technical reasons.

The pressure-flow results for liquid and viscous swallows are summarized in Table 6.2.

Effect of peristaltic break size on PFA metrics during viscous swallowing When comparing only those subjects with intact peristalsis (ICD <2 cm), IBP was higher in older subjects when compared with young (23.5 ± 8.7 mmHg vs 11.4 ± 0.7 mmHg, p = 0.03).

The IR, a marker of bolus retention, was significantly increased (O: 0.50 ± 0.01 vs YC: 0.30 ± 0.01; p = 0.005) in older subjects with intact peristalsis, as compared with YCs.

In those subjects with peristaltic breaks in excess of 2 cm (ICD >2 cm), a higher mean PeakP occurred in younger controls (39.2 ± 2.8 mmHg vs 27.2± 4.5 mmHg; p = 0.03), while the rate of pressure increases, IBP slope (O: 6.8 ± 1.3 mmHg/s vs YC: 4.0 ± 0.5 mmHg/s; p = 0.03) and pressure-flow index (36.1 ± 6.8 vs 15.8 ± 2.7; p = 0.006) were increased in the older subjects. Older subjects again had a significantly higher IR (0.60 ± 0.01 vs 0.40 ± 0.01).

6.3.2 Relationships between esophageal motility parameters and pharyngeal function

Complete data on pharyngeal and esophageal measures were available for 29 YCs and 13 older subjects.

Table 6.1 Chicago variables for liquid and viscous swallows in the upright posture P-value data are unpaired t-tests

	Liquids (5ml)						Viscous (5ml)					
	Mean	**SEM**	**Median**	**P5**	**P95**	**p-value**	**Mean**	**SEM**	**Median**	**P5**	**P95**	**p-value**
IRP4 (mmHg)												
YC	8.0	0.9	8.0	0.9	14.8	0.7	7.6	0.9	7.0	0.5	16.6	**0.002**
O	8.9	1.5	9.0	0.3	17.6		14.5	2.1	16.0	1.3	25.0	
ICD (cm)												
YC	2.1	0.5	1.0	0.0	7.6	0.05	2.0	0.5	0.2	0.1	7.5	**0.03**
O	4.4	1.2	1.2	0.1	12.0		4.8	1.5	1.5	0.1	13.3	
CFV (cm/s)												
YC	3.5	0.18	3.2	2.4	5.5	**0.004**	2.8	0.1	2.7	2.1	3.4	**0.003**
O	6.2	1.2	3.6	2.2	14.7		5.2	1.1	3.7	2.1	12.6	
DCI (mmHg.s.cm)												
YC	766.9	123.1	668.5	85.0	1688.7	0.87	701.5	119.3	550.0	44.1	1827.8	0.31
O	728.5	224.0	495.0	4.8	2363.0		1050.5	427.5	340.5	21.7	3737.4	
DL (s)												
YC	6.01	0.2	6.2	4.2	8.3	0.6	6.7	0.2	6.8	4.2	8.7	0.2
O	6.3	0.3	6.4	4.2	8.0		6.0	0.6	6.2	2.6	8.3	

IRP4, 4-s integrated relaxation pressure; ICD, isocontour defect; CFV, contractile front velocity; DCI, distal contractile integral; DL, distal latency. Bold text indicates significant p-values.
Average of five swallows per individual

Table 6.2 Impedance/pressure metrics derived from AIMplot analysis P-values are unpaired t-tests

	Liquids (5ml)						Viscous (5ml)					
	Mean	**SEM**	**Median**	**P5**	**P95**	**p-value**	**Mean**	**SEM**	**Median**	**P5**	**P95**	**p-value**
PeakP (mmHg)												
YC	66.64	5.80	63.60	28.05	108.54	0.33	64.54	5.55	63.18	29.42	103.27	0.9
O	55.61	8.85	57.28	19.49	111.97		63.03	14.38	41.62	20.43	172.09	
PNadImp (mmHg)												
YC	4.32	0.23	4.38	2.25	6.19	0.17	7.01	0.50	6.79	3.09	11.73	**0.04**
O	8.66	8.85	3.83	0.74	27.48		14.06	5.00	10.59	1.86	38.48	
IBP (mmHg)												
YC	5.66	0.46	5.28	2.44	10.54	0.13	9.90	0.65	10.27	4.80	16.54	0.05
O	10.50	4.45	5.15	2.38	30.92		17.30	5.29	12.52	5.54	43.21	
IBP Slope (mmHg/s)												
YC	4.60	0.97	2.34	0.11	17.15	0.49	8.01	0.96	6.39	2.64	16.97	**0.02**
O	3.57	4.52	2.95	0.06	7.65		17.3	5.2	8.09	3.79	19.00	
TNIPP (s)												
YC	4.01	0.2	3.80	2.83	5.66	0.07	2.72	0.09	2.67	1.98	3.69	0.3
O	4.50	0.2	4.54	3.28	5.52		2.90	0.21	2.91	1.76	4.05	
PFI												
YC	64.42	21.04	10.14	0.32	337.08	0.3	65.30	14.78	26.39	9.50	246.69	0.99
O	34.87	0.20	4.76	0.52	105.28		65.19	27.34	38.80	2.32	219.06	
IR												
YC	0.27	0.02	0.26	0.13	0.46	**0.002**	0.36	0.01	0.35	0.22	0.50	**<0.001**
O	0.42	0.05	0.3	0.24	0.76		0.56	0.03	0.59	0.32	0.72	

*Units are mmHg/s. PeakP, peak pressure; IBP, intrabolus pressure; TNIPP, time of nadir impedance to peak pressure; PFI, pressure-flow index; IR, impedance ratio. Bold text indicates significant p-values. *Average of five swallows per individual.*

The swallow risk index (SRI), a measure of pharyngeal dysfunction that correlates with radiological aspiration, was above 15 (the previously determined cutoff for dysfunction)4 in one subject in each age group during liquid swallows, and four older subjects with viscous bolus. Three of these older subjects had failed esophageal peristalsis, while the remaining subject had ineffective esophageal motility. Fig. 3A compares the SRI in YC and older subjects with failed (OF) and normal (OC) peristalsis with viscous bolus. The median SRI was significantly higher in OF (18[5;25]) when compared with YC (2[1;4]; p = 0.02). In older subjects, the SRI correlated positively with peristaltic break size (r = 0.65; p = 0.004) and negatively with DCI for viscous bolus (r = 0.50; p = 0.01).

Furthermore, older subjects with failed peristalsis (OF) during viscous swallows (Fig. 3B) had evidence of reduced UES distention, as indicated by a lower maximum admittance when compared with YC (3.0 ± 0.2 vs 4.5 ± 0.3 ms; p < 0.001). Admittance was also lower in older patients with normal peristalsis (3.6 ± 0.3 ms; p = 0.02). Admittance correlated negatively with peristaltic break size (r = 0.66; p < 0.001) and positively with DCI (r = 0.71; p < 0.001).

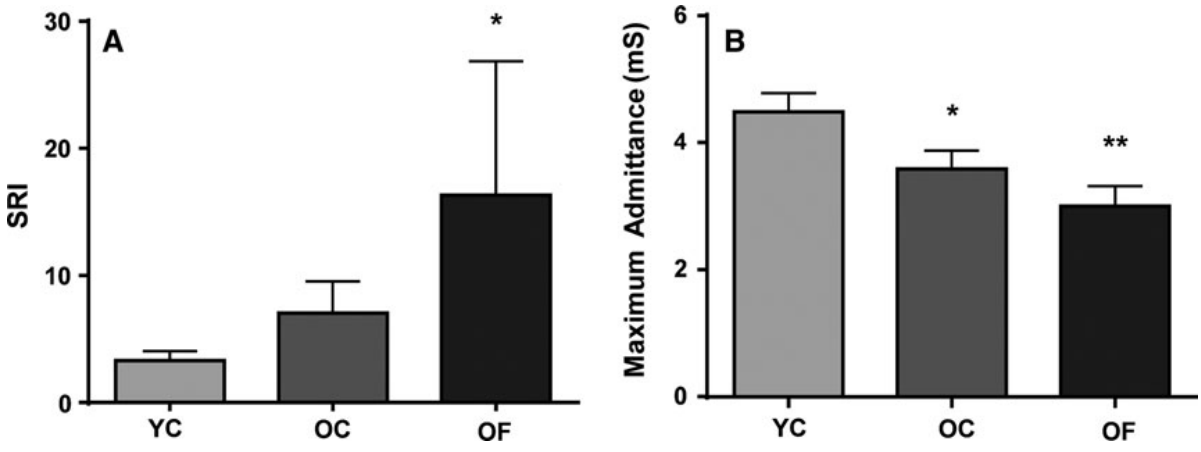


Figure 6.3 Relationship between pharyngeal function and oesophageal variables with viscous bolus. (A) Increased swallow risk index (SRI) in older subjects with failed (OF) and normal (OC) peristalsis, when compared with young controls (YC). (B) Reduced upper oesophageal sphincter (UOS) distention, as indicated by a lower maximum admittance, in older subjects with either failed (OF) or normal (OC) peristalsis when compared with younger controls (YC). *p = 0.02; **p < 0.001; vs YC.

6.3.3 Bolus clearance

Clearance of liquid bolus was significantly lower in asymptomatic older subjects (60%) when compared with younger controls (82%) during upright swallowing (v2 = 4.935; p < 0.05). There

was an even more marked reduction with viscous bolus, with successful clearance achieved in 83% of younger controls and only 40% of older subjects (v2 = 39.08; p < 0.001; Fig. 4).

Fig. 5 shows Chicago classification and PFA metrics for YC and older subjects (O) with and without bolus clearance.

During two-way ANOVA, longer peristaltic breaks (F = 17.21; p < 0.001) and rapid peristalsis (F = 14.155; p < 0.001) were strongly associated with failed liquid clearance in the older group. Measures indicating decreased peristaltic vigor (DCI, mean peakP) were associated with failed clearance in both groups.

For viscous bolus, longer peristaltic breaks (F = 7.129; p = 0.009) and rapid peristalsis (F = 4.502; p < 0.05) were again associated with failed clearance, while decreased peristaltic vigor (DCI, F = 18.646; p < 0.001) and lower IBP (F = 8.088; p = 0.006) were also associated with failed clearance in the older group, when compared with YCs.

Increased IR was observed in both groups during failed clearance.

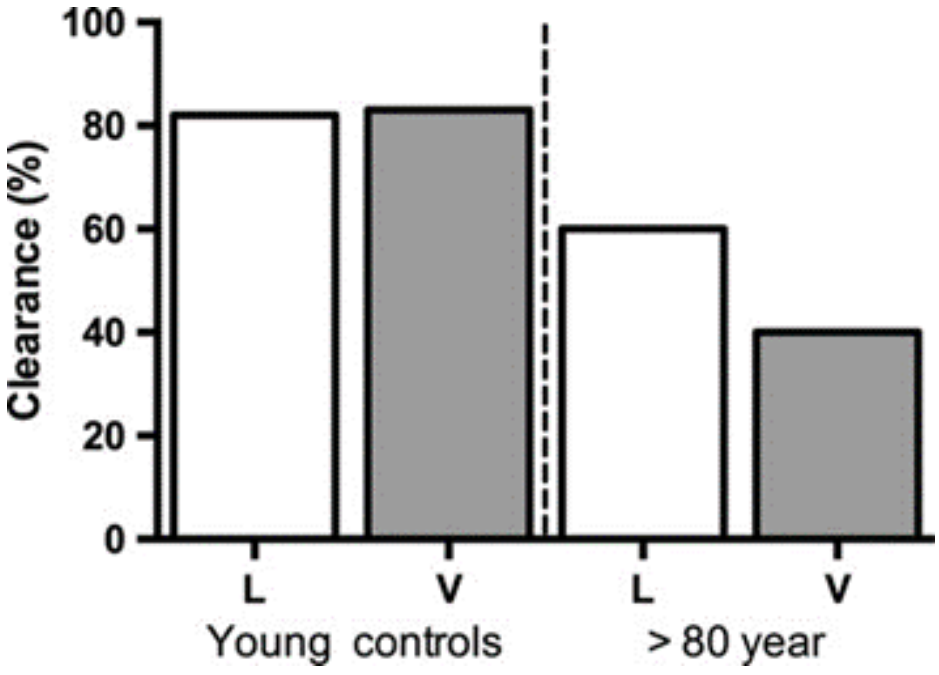


Figure 6.4 Percent bolus clearance for young controls and older subjects during liquid (L) and viscous (V) swallowing in a sitting posture.

Discussion

This is the first study to perform PFA in addition to EPT in the esophagus to determine subtle changes in esophageal physiology that occur with healthy aging. As previously shown, asymptomatic individuals at the extreme of age have evidence of impaired oropharyngeal swallowing when studied using PFA.4 This study extends this approach to the esophagus to study those at extreme older age (over 80 years). Our results show that, in addition to impaired oropharyngeal function, asymptomatic older subjects also have impaired esophageal function leading to failed bolus transit, which is most pronounced with increasing bolus consistency[31]. Furthermore, the impairment of oropharyngeal and esophageal function tended to occur in the same individuals.

Older individuals have a greater proportion of failed swallows when compared with YCs. Although there is significant debate in the literature, it is widely assumed that esophageal motor function deteriorates in older age. Studies in healthy volunteers (aged between 20 and 90 years) and some patient cohorts have shown decreased peristaltic activity, both primary and secondary, and reduced esophageal compliance with advancing age[7,9,32-36]. There are conflicting data on whether peristaltic amplitude is reduced[35,36], increased[37], or remains unchanged[38] in older age. Using the newer measure of DCI, our study supports the latter with no difference in contractile vigour observed between the young and older group (when successful peristalsis was achieved). However, a reduced DCI remained a correlate of failed clearance in both groups in our study, and the previous findings suggesting decreased peristaltic vigour may simply reflect a greater proportion of asymptomatic older subjects with failed or ineffective esophageal motility. Longer peristaltic breaks in excess of 2–5 cm, a known correlate of failed bolus clearance[26,29] were seen in many older individuals and the mean peristaltic break length was increased for both liquid and viscous swallows (Table 6.1).

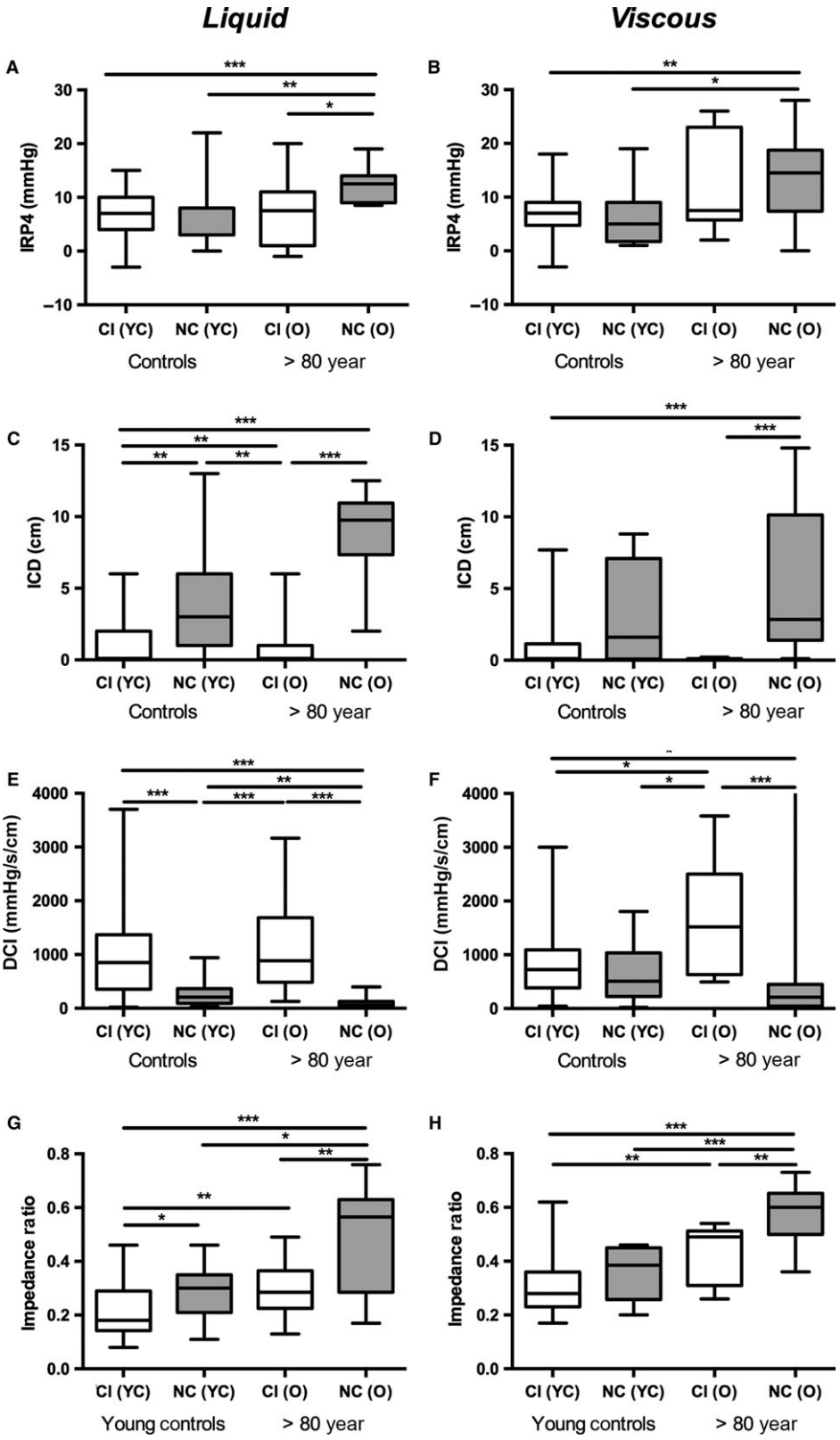


Figure 6.5 Esophageal pressure topography and pressure-flow analysis in young controls (YC) and older asymptomatic subjects (O) for cleared (Cl) and non-cleared (NC) bolus.

We have previously shown abnormal LOS function in individuals over 80 years, as evidenced by higher resting pressure and incomplete relaxation[11], which is consistent with an earlier study by Ren et al.[32] Other studies, however, have been unable to demonstrate any age effects on the LOS.[12,38] In this study, a higher IRP4 was observed during viscous swallows in the healthy older group (Table 1). Furthermore, distal esophageal intra-bolus pressures were increased during both liquid and viscous swallows (Table 2), and the intra-bolus pressure slope (reflecting the rate at which pressure increases) was also higher with viscous bolus in this older cohort. These findings are in keeping with EGJ outflow resistance increasing with age. In concert with longer peristaltic breaks, the presence of EGJ outflow obstruction and consequent increased intrabolus pressures lead to a high likelihood of proximal bolus escape leading to failed bolus clearance as witnessed in our study. Although elevations in distal intrabolus pressures have previously been associated with increasing bolus perception[18], this was not the case in our older cohort and one could postulate a decline in the activation of sensory afferent pathways in this group. The previously reported decrease in distal esophageal distensibility[9] is supported by the increased intrabolus pressures observed in the older group. We postulate that reduced distensibility of the distal esophagus, associated with decreased bolus presence, leads to less peripheral activation of stretch receptors, involved in LOS relaxation[39]. It is, however, also possible that reduced LOS opening in older subjects are additionally the result of mechanical factors or incoordination of central and peripheral LOS relaxation. The 95th percentile for our younger group for IRP was 14.8 mmHg, which is lower than that previously described for this device in the supine posture.[40] We postulate that this difference occurs as a result of an upright posture. Do Carmo et al.[41] had previously described a lower IRP in the sitting vs supine posture in healthy volunteers, using high-resolution solid-state manometry using an assembly from a different manufacturer (13.5 vs 6.4 mmHg). Lower pressures may also be observed with thinner diameter catheters. Our results must be interpreted with caution due to the small sample size, and further studies are needed to elucidate the causes of EGJ dysfunction in the aged.

Esophageal PFA is a novel approach aimed at detecting additional abnormalities not evident with EPT. This approach has been used in studying patients with post-fundoplication dysphagia[15] and non-obstructive dysphagia[16,17]. Among several metrics produced by the analysis, the pressure-flow index and IR have proved useful in classifying individuals within a pressure-flow matrix, which assesses bolus pressurization and clearance. Fig. 6.6 is a pressure-flow matrix of the findings of our study for both younger controls and older subjects. Esophageal PFA performed in healthy older subjects demonstrates diminished clearance (higher IR) and/or augmented pressures relative to flow (higher PFI), resulting from decreased peristaltic integrity and/or reduced LOS relaxation. Of interest, the IR was increased for older cohorts with and without impaired bolus clearance by standard criteria. This is in keeping with imaging studies, which have shown an increased frequency of intraesophageal stasis10 and incomplete esophageal emptying[31] with both liquid and viscous swallows in asymptomatic volunteers aged above 65 years. Standard impedance criteria used to date may not be entirely reliable in determining bolus clearance when compared to radiological findings, particularly in the case of failed contractions[42], as seen frequently in our older cohort. Impedance ratio may represent a superior measure of bolus clearance in this context[21].

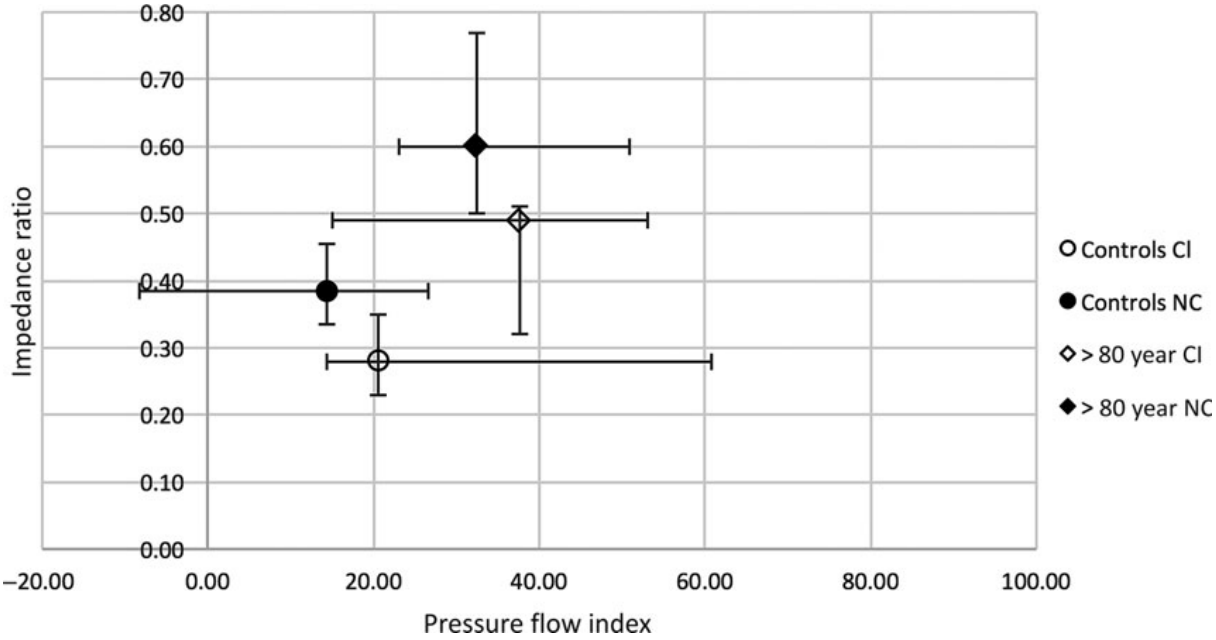


Figure 6.6 Pressure-flow matrix for young controls and older subjects during viscous swallows. Impedance ratio is markedly increased in older subjects indicating bolus residue and retention.

The finding of impaired oropharyngeal and esophageal function in the same older individuals are interesting, especially considering that subjects are asymptomatic. To our knowledge, this is the first description of abnormal pharyngeal measurements in subjects with evidence of esophageal dysfunction. We are cautious in our interpretation of this finding in this cohort due to the small sample size. It is possible that a similar pathophysiological process such as decreased or abnormal swallow program generator and/or vagal activation or a loss of sensory modulation of swallowing could cause abnormalities in both oropharyngeal and esophageal function. Another possibility, supported by the finding that 'dual dysfunction' is confined to bolus of increased consistency, is that a combination of reduced pharyngeal 'pump' function and UES distensibility leads to a decreased bolus presence in the distal esophagus. As a consequence, there is less bolus-based distention and decreased activation of the peripheral 'neuromechanical loop'[43,44] via distal esophageal mechanoreceptors, leading to peripheral failure of 'primary peristalsis'. Regardless, combined oropharyngeal and esophageal dysfunction is intriguing and worthy of further study.

Our study has several limitations. Upright manometry is not typically performed and may limit the applicability of our findings. In this posture, bolus transport is aided by gravity,45 and consequently, less peristaltic contribution is needed to assist clearance. This is particularly true for liquid and forms the premise for performing esophageal manometry using liquid swallows in the supine posture. Despite this, liquid clearance was impaired in association with longer peristaltic breaks in our older subjects. Expanded protocols including increased consistencies and upright posture are becoming more commonplace as a correlate of physiological swallowing, and thus using this posture may also potentially be a strength of our study. The catheter specification (25 cm length) used for this study required repositioning in the majority of individuals in order to capture the complete distal esophagus from the transition zone to proximal stomach. Although this was achieved, it meant that a drop in impedance at the most proximal channel was used to define swallow onset, which may shorten the DL. Despite this limitation, distal latencies described are consistent with those obtained using a longer catheter with the same recording system[7,40]. Lastly, the difference in Chicago variables

with older age may be overestimated by the use of mean ± SEM due to the wide variation in older subjects.

In conclusion, our study of asymptomatic individuals over 80 years of age showed ineffective and failed peristalsis, rapid contractions with a normal latency, and decreased LOS relaxation. Impaired bolus clearance occurs frequently and is increased for viscous over liquid consistency.

Chapter 7 Age-related impairment of oesophagogastric junction relaxation and bolus flow time

As published

Abstract

Aim To investigate the functional effects of abnormal oesophagogastric (OGJ) measurements in asymptomatic healthy volunteers over eighty years of age.

Methods Data from 30 young controls (11 M, mean age 37 ± 11 years) and 15 aged subjects (9 M, 85 ± 4 years) were compared for novel metrics of OGJ-function: OGJ- contractile integral (OGJ-CI), "total" OGJ-CI and bolus flow time (BFT). Data were acquired using a 3.2 mm, 25 pressure (1 cm spacing) and 12 impedance segment (2 cm) solid-state catheter (Unisensor and MMS Solar GI system) across the OGJ. Five swallows each of 5 mL liquid (L) and viscous (V) bolus were analysed. Mean values were compared using Student's t test for normally distributed data or Mann Whitney U-test when non-normally distributed. A P value < 0.05 was considered significant.

Results OGJ-CI at rest was similar for older subjects compared to controls. "Total" OGJ-CI, measured during liquid swallowing, was increased in older individuals when compared to young controls (O 39 ± 7 mmHg.cm vs C 18 ± 3 mmHg.cm; P = 0.006). For both liquid and viscous bolus consistencies, IRP4 was increased (L: 11.9 ± 2.3 mmHg vs 5.9 ± 1.0 mmHg, P = 0.019 and V: 14.3 ± 2.4 mmHg vs 7.3 ± 0.8 mmHg; P = 0.02) and BFT was reduced (L: 1.7 ± 0.3 s vs 3.8 ± 0.2 s and V: 1.9 ± 0.3 s vs 3.8 ± 0.2 s; P < 0.001 for both) in older subjects, when compared to young. A matrix of bolus flow and presence above the OGJ indicated reductions in bolus flow at the OGJ occurred due to both impaired bolus transport through the esophageal body (i.e., the bolus never reached the OGJ) and increased flow resistance at the OGJ (i.e., the bolus retained just above the OGJ).

Conclusion Bolus flow through the OGJ is reduced in asymptomatic older individuals. Both ineffective esophageal bolus transport and increased OGJ resistance contribute to impaired bolus flow.

7.1 Introduction

The oesophagogastric junction (OGJ) is an anatomically and physiologically complex region, with several functions such as preventing gastro esophageal reflux, while being able to allow bolus passage during swallowing, evacuation of air during belching or gastric contents during vomiting [1-3]. The OGJ consists of a combination of the lower esophageal sphincter (LES) and diaphragmatic crura. The LES may be anatomically aligned with the crural diaphragm (CD) or misaligned in the form of a hiatus hernia. The lower esophageal sphincter is a smooth muscle region in the lower esophagus, tonically contracted at rest, but with the capacity for swallow, reflex or distention- based relaxation [1,2]. The LES receives vagal input from the brainstem via myenteric non-adrenergic non- cholinergic neurons [4], which release primarily nitric oxide, but also vasoactive intestinal peptide in order to induce LES relaxation [5,6]. Passage of bolus through the OGJ region requires relaxation of the LES, aided by distraction of the LES region and CD by contraction of distal esophageal longitudinal muscle. The CD is thus an important constituent of the OGJ and therefore the term OGJ is thus preferred over LES to functionally describe this region [1].

The use of high-resolution manometry and the Chicago classification system for the description of esophageal pressure topography has necessitated the development of novel measures for the anatomical description of the OGJ, but also for the assessment of barrier function, swallow-induced relaxation and functional bolus clearance at the OGJ. Several novel metrics have been described in order to measure these different functional aspects at the OGJ. In terms of its barrier function at rest (preventing gastroesophageal reflux disease - GERD), the metric oesophagogastric contractile integral (OGJ-CI) has been shown to be superior to other OGJ metrics in distinguishing GERD patients with and without proton-pump inhibitor response [7,8], as well as distal esophageal acid exposure [9] and could differentiate patients with achalasia or anti-reflux surgery from controls[10]. For the assessment of swallow induced OGJ relaxation, Pandolfino et al. [11] described the integrated relaxation pressure in four seconds (IRP4). This measure and specifically the time interval chosen, was shown to be superior to other iterations of IRP or metrics describing OGJ relaxation of clinical relevance

[11,12]. More recently Lin et al. [13,14] described the novel metric bolus flow time (BFT) at the OGJ. This metric determines bolus clearance at the OGJ and is reduced in achalasia [13] or other circumstances denoting reduced bolus clearance through the OGJ, such as ineffective esophageal motility [14].

We have recently described changes in the distal esophagus of individuals aged over eighty years, including reduced peristaltic vigour and clearance [15], as well as reduced OGJ relaxation in both healthy and dysphagic aged individuals [16-18]. Both reduced clearance and decreased OGJ relaxation mimic the circumstances under which a reduced bolus flow time had previously been described by Lin et al. [13,14] and it would thus be of value to further assess OGJ function in the aged population, using the BFT. Furthermore, it is known that older individuals have reduced symptoms in relation to the severity of gastroesophageal reflux disease[19] and thus an assessment of OGJ barrier function would be additionally useful in this population, but the recent descriptions of OGJ barrier function metrics have not been assessed in this age cohort.

The aims of this study were to evaluate different aspects of oesophagogastric junction function in asymptomatic individuals over eighty years of age compared to young controls: (1) OGJ barrier function at rest through the novel metric OGJ-CI; (2) Swallow induced OGJ-relaxation through the Chicago classification metric integrated relaxation pressure (IRP4); and

(3) OGJ bolus flow through the pressure-flow metric bolus flow time (BFT) and bolus presence in the distal esophagus through bolus presence time (BPT).

7.2 Materials and Methods

7.2.1 Study Participants

Forty-five healthy volunteers (20 M, aged 20-93 years) were recruited through community advertisement. A screening history was performed in all subjects to exclude (1) past or present swallowing difficulties; (2) symptoms suggestive of a motility disorder; (3) upper gastrointestinal conditions including gastro- esophageal reflux disease; (4) diabetes mellitus; (5) previous history of gastrointestinal surgery; and (6) prescription medications known to

affect GI motility. To further exclude underlying dysphagia, all potential subjects performed a previously validated Dakkak questionnaire [20] to assess the esophageal phase of swallowing for different food consistencies. Only subjects with a normal score were included in the study. Body weight and height, and current or past smoking history were also recorded. Enrolled subjects were stratified into the following two groups: younger controls and older subjects (> 80 years).

The study protocol was approved by the Southern Adelaide Clinical Human Research Ethics Committee (Approval No. 403.10). All participants gave written informed consent prior to enrolment, and studies were performed at the Repatriation General Hospital, Daw Park, South Australia. AIM pressure-flow analysis of the pharynx [21] and distal esophagus [15] had previously been reported in this cohort of subjects.

7.2.2 Measurement technique

Subjects were studied in a sitting posture using an MMS Solar (Solar GI acquisition system, MMS, Enschede, The Netherlands) manometric assembly with a 10 French (3.2 mm diameter) unidirectional catheter (Unisensor Inc, Attikon, Switzerland) with 25 pressure (1cm spaced) and 12 impedance segments (2 cm length) straddling the oesophagogastric segment with at least 2-3 sensors in the stomach. Pressure and impedance data were recorded at 20Hz.

7.2.3 Study Protocol

Following nasal administration of co-phenylcaine forte spray and 2% lignocaine gel, subjects were intubated with the sensors in a posterior orientation. The HRIM assembly was positioned with the recording segment spanning the esophageal transition zone to proximal stomach. Following a 10-min accommodation period, subjects received five 5ml and 10 mL boluses of liquid (0.9% NaCl) and standardized viscous bolus (EFT Viscous Swallow Challenge Medium, viscosity 13000 cP; Sandhill Scientific, Denver, Co. United States) via a syringe and asked to swallow once on cue. Studies were performed in the upright posture with head in a neutral position.

7.2.4 Determination of OGJ-CI

Method for the determination of OGJ-CI is described in Figure 7.1. OGJ-CI was measured by assessing OGJ function in the rest period, i.e., prior to the onset of swallowing boluses. During calculation of the OGJ-CI, OGJ pressure was measured relative to intra gastric pressure, as the distal esophageal/gastric pressure differential is an important determinant of distal esophageal acid reflux [22]. The isobaric contour was set at +2 mmHg above the intra gastric pressure, as per Jasper et al. The distal contractile integral “box” was then placed around a three-respiratory cycle segment, starting with diaphragmatic contraction. The value obtained in the box (mmHg.s-1.cm-1) was divided by the total duration of the three respiratory cycles to calculate OGJ-CI (mmHg.cm-1). “Total” OGJ-CI [23] was determined by calculating the measurement within a “DCI”-box at the OGJ, using the 2 mmHg above intra gastric pressure isobar contour, during ten liquid swallows and dividing this value by the total duration in seconds.

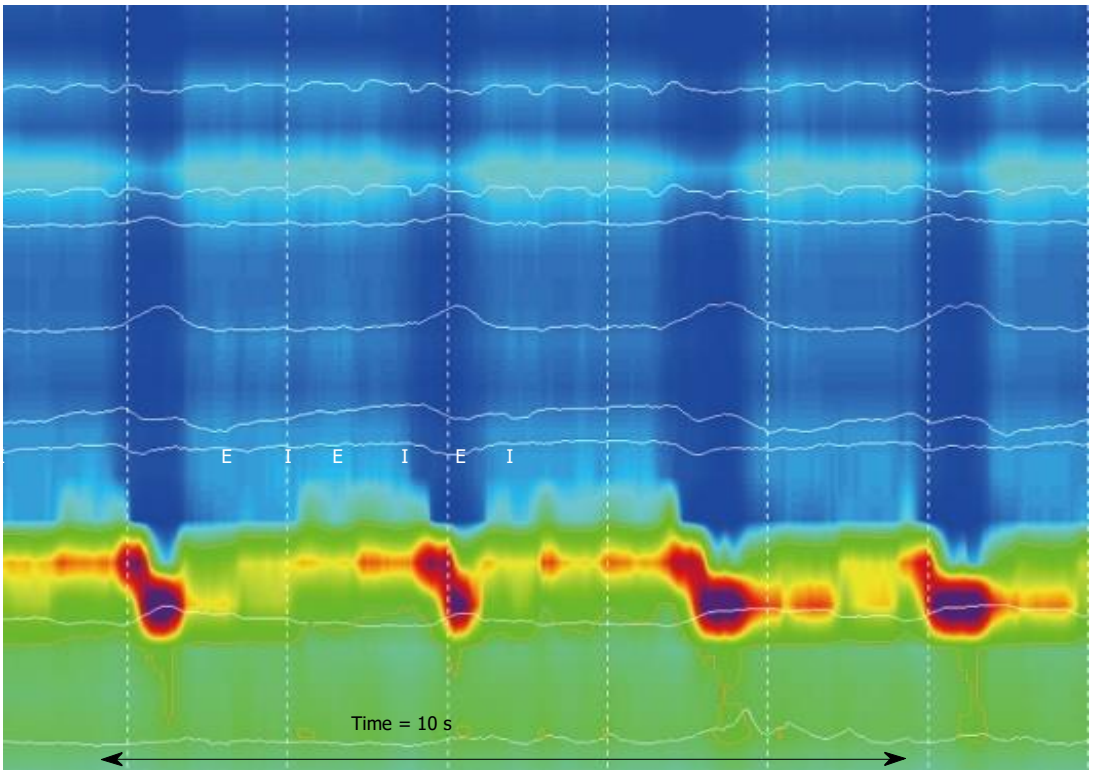


Figure 7.1 Method for determining esophagogastric junction contractile integral. Inspiration (I) and expiration (E) are pictured for the intra thoracic portion above the OGJ (respiratory inversion pictured as dotted white line). Isobaric contour tool is adjusted to 2 mmHg above the intra gastric pressure to determine the boundaries for the OGJ. The “DCI box” (dotted red) is placed around the OGJ starting at the diaphragmatic contraction (mid-point inspiration) and extended for 3 further respiratory cycles. The “DCI”-value is then divided by time to determine OGJ-CI in mmHg.cm. OGJ: Esophagogastric junction.

7.2.5 Swallow-induced OGJ relaxation

Swallow induced OGJ relaxation was determined during liquid and viscous swallows by measuring the integrated relaxation pressure in four seconds at the OGJ. This value is determined as the lowest pressure for four contiguous or non-contiguous seconds within the ten seconds following swallow-induced LES relaxation, measured from UES onset, where visible, or impedance drop below 90% of the resting value at the most proximal impedance segment. In practice the IRP tool in the MMS software was used for this measurement. IRP4 is expressed in mmHg.

7.2.6 Measurement of bolus flow time and presence time

Method for the determination of bolus flow time (BFT) is described in Figure 7.2. Bolus flow time was determined based on the method originally described by Lin et al[14]. Text files were exported as thirty second segments including the swallow sequences. These files were then imported into Matlab and analysed using an adapted version of the script esophageal AIMplot version 5.0 (T.Omari, Flinders University; Adelaide, Australia). The methodology for esophageal AIMplot pressure flow analysis is described elsewhere [15,24,25]. Specifically, as relates to the measurement of BFT and BPT the method is as described below (Figure 2):

A virtual e-sleeve of pressure and impedance data at the OGJ was created. Pressure at the most proximal pressure channel in this region and intragastric pressure was used as reference values to determine bolus flow and directionality of such flow. Bolus flow from the esophagus to the stomach was determined to have occurred (with the commensurate time included in the BFT) when: (1) Impedance in the three impedance segments at and above the level of the OGJ dropped to below 90% of baseline (without having returned above 50% at which point flow ceases); (2) Pressure at the OGJ dropped to below 50% of baseline; and (3)

Diaphragmatic crural contraction pressures were below 10 mmHg and remained at less than 50% of the baseline. Bolus flow time and bolus presence time were reported in seconds. Impedance ratio is reported as implied as a ratio of the impedance at maximal luminal occlusion to that at maximal luminal distention.

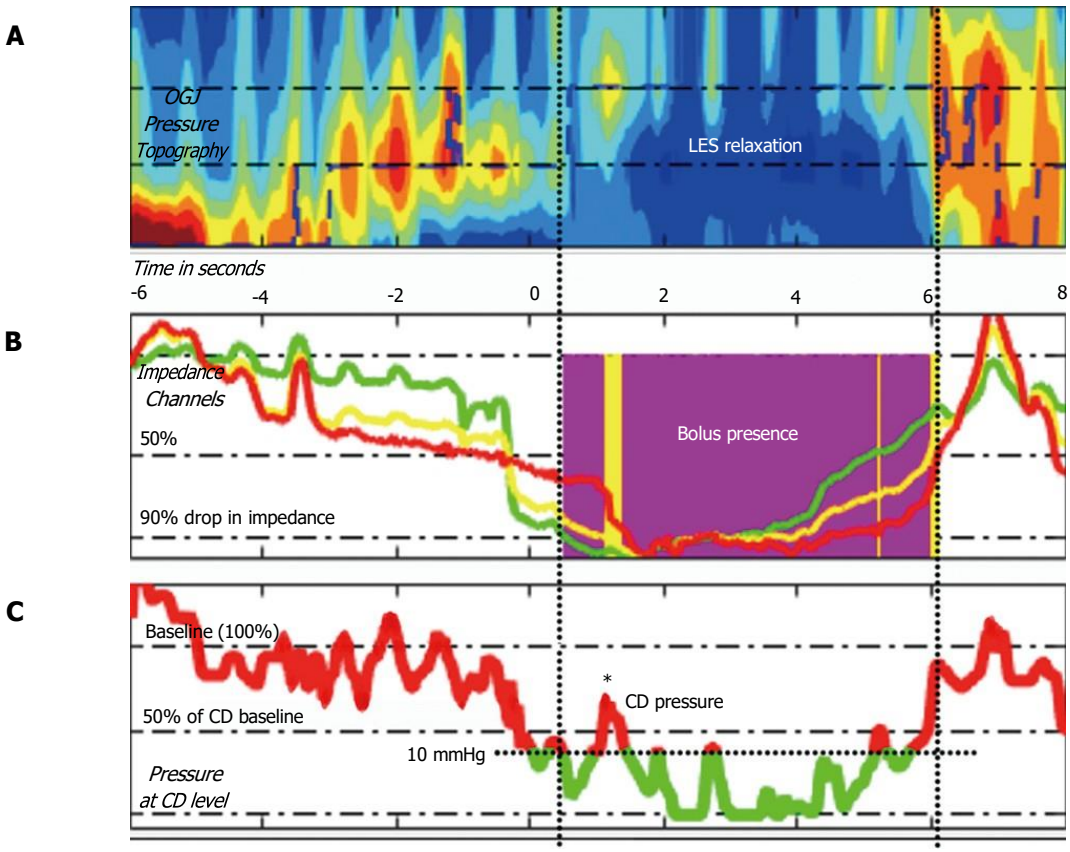


Figure 7.2 Method for determining bolus flow time at the oesophagogastric junction using pressure impedance data (modified from Lin 2014). A: Esophageal pressure topography of region of interest at OGJ; B: Bolus flow is determined as occurring at the OGJ when the distal esophageal impedance drops below 90% of baseline until impedance returns above 50% baseline (purple area), provided pressure criteria are simultaneously met at the crural diaphragm (CD) position; C: Pressure above 10 mmHg and 50% peak pressure inhibits bolus flow at CD position despite impedance criteria being met (* - corresponding with yellow area in B).

7.2.7 Statistical analysis

Data were analysed using Sigmaplot 13 (Systat Software Inc., San Jose, CA, United States) and Prism Plus 6.0 (Graphpad, San Diego, CA, United States). Data was assessed for a normal distribution using the D'Agostino & Pearson omnibus test. Pairwise comparisons were

done via independent sample t-test or Mann Whitney U-test when non-normally distributed. Fisher's exact test was done to compare the proportions of subjects with different OGJ-subtypes. Data presented are mean ± SEM. A P value of < 0.05 considered statistically significant.

7.3 Results

7.3.1 Subjects

Characteristics of study participants are included in Table 1. All subjects tolerated the study procedure well and no adverse events were reported. The mean age of older subjects (n = 15; aged 85 ± 4 years, 9 M) was significantly higher than the younger group (n = 30; aged 37 ± 11 years, 11 M) (P < 0.001).

Table 7.1 Characteristics of control and asymptomatic older subjects n (%)

	Control	Older	*P* value
Number (M/F)	30 (11/19)	15 (9/6)	0.14
Age ± SD (range)	37 ± 11 (21-58) yr	85 ± 4 (80-93) yr	< 0.001
OGJ subtype			0.69
Ⅰ	18 (60)	9 (60)	
Ⅱ	9 (30)	3 (20)	
Ⅲa	1 (3)	1 (7)	
Ⅲb	2 (7)	2 (13)	
Proximal margin OGJ (cm)	43 ± 0.6	45 ± 1	0.06
Overall length OGJ[1] (cm)	3.2 ± 0.2	3.4 ± 0.3	0.34

[1] OGJ Type III were excluded from calculation of total length. OGJ: Oesophagogastric junction; Ave five swallows per individual

7.3.2 OGJ subtype

There was no significant difference in the distribution of OGJ subtypes between controls and older subjects in a sitting posture (Table 7.1). Specifically, there was no increase in the Type III OGJ, associated with hiatus hernia, in the older subjects.

7.3.3 OGJ Barrier Function and OGJ-CI

Examples of OGJ-CI calculation are shown in Figure 7.3. OGJ-CI was similar for older subjects (O) compared to younger controls (C) (O 34 ± 5 mmHg.cm vs C 25 ± 5 mmHg.cm, P = 0.18). Three older and six control subjects (20%) had OGJ-CI values below 20 mmHg. cm, within

the range previously shown to be associated with gastro esophageal reflux disease[8]. Intragastric pressure was higher in older subjects compared to the younger group (Liquid: O 9 ± 2 mmHg vs C 2 ± 2 mmHg, P = 0.002; Viscous: O 11 ± 2 mmHg vs C 4 ± 2 mmHg, P = 0.005). Due to decreased swallow- induced relaxation, "total" OGJ-CI was increased in older individuals when compared to young controls (O 39 ± 7 mmHg.cm vs C 18 ± 3 mmHg.cm; P = 0.006).

7.3.4 OGJ swallow-induced relaxation

Examples of OGJ swallow-induced relaxation are shown in Figure 7.4. The OGJ relaxation pressure (IRP4) was significantly higher in older adults for both liquid (P = 0.02) and viscous (P = 0.02) swallows, when compared to the younger group (Table 2). Age had no effect on the nadir OGJ pressure for either bolus consistency. Despite increased IRP, older individuals did not display the oesophagogastric outflow obstruction phenotype as defined by an increase in intrabolus pressure at the 30-mmHg isobar contour.

7.3.5 OGJ bolus flow

Data for OGJ bolus presence time (BPT) and bolus flow time (BFT) are shown in Table 2 and examples are shown in Figure 7.5. Bolus flow time is markedly reduced in older individuals for both consistencies (P < 0.001). There was a negative correlation between BFT and the IRP4 (r = -0.42, P = 0.02) for all subjects. Bolus flow time was lowest in older subjects with reduced impedance-based clearance (Figure 7.6).

Table 7.2 Oesophagogastric junction metrics during swallowing

	Liquid swallows			Viscous swallows		
	Control	Older	*P* value	Control	Older	*P* value
IRP4 (mmHg)	5.9 ± 1.0	11.9 ± 2.3	0.02	7.3 ± 0.8	14.3 ± 2.4	0.02
GasP (mmHg)	2.2 ± 1.5	9.4 ± 1.6	0.002	4.1 ± 1.6	11.2 ± 1.7	0.005
BPT (s)	5.5 ± 1.0	3.9 ± 0.5	0.01	4.5 ± 0.2	4.3 ± 0.5	0.19
BFT (s)	3.8 ± 0.2	1.7 ± 0.3	< 0.001	3.8 ± 0.2	1.9 ± 0.3	< 0.001
Average for five swallows per individual						

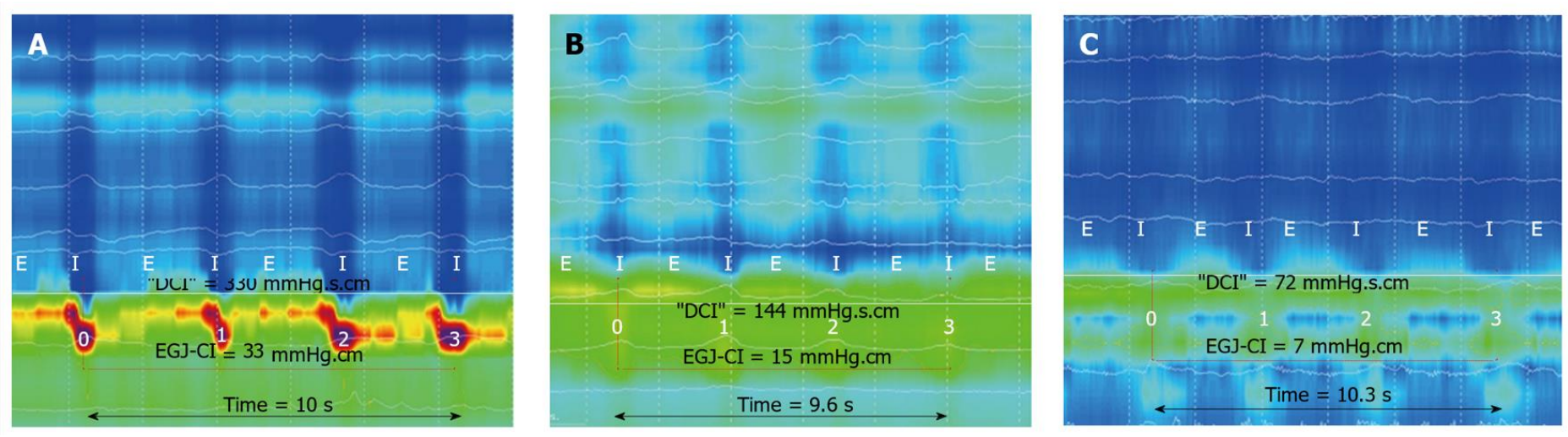


Figure 7.3 Examples of esophagogastric junction-contractile integral in 3 individuals; an (A) 85-year-old, (B) 50-year-old and (C) 22-year-old. In addition to different OGJ-CI measurements, three different OGJ subtypes are displayed as subtypes I (A), II (B) and IIIb (C). Expiration (E) and inspiration (I) are pictured overlaying the thoracic recording, while pressure inversion is indicated by a solid white line.

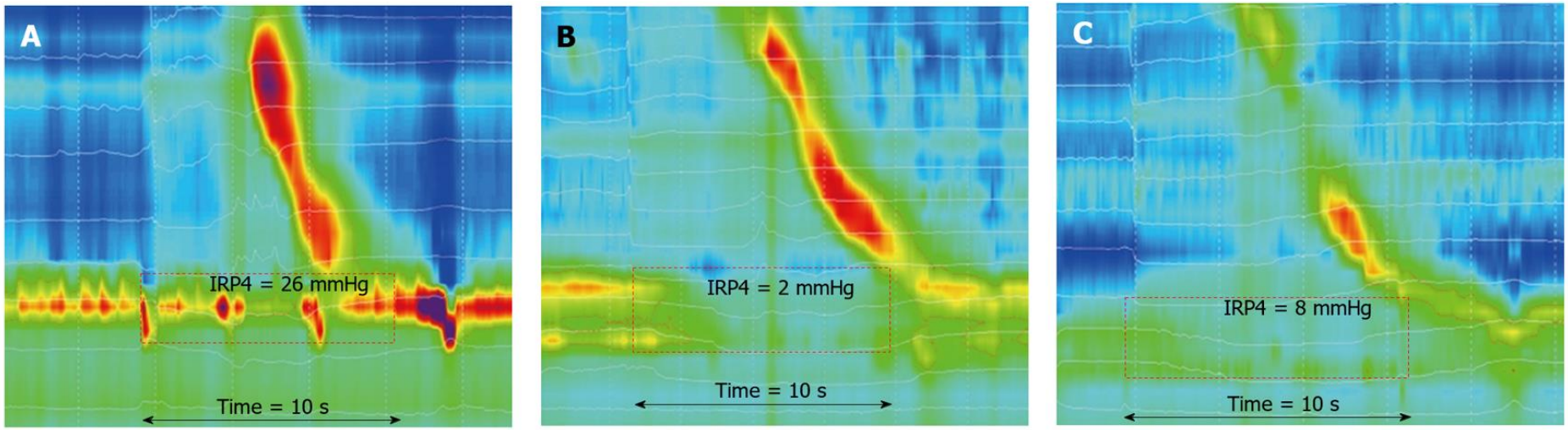


Figure 7.4 Examples of 4 second integrated relaxation pressure in the same subjects in Figure 7.3; an (A) 85-year-old, (B) 50-year-old and (C) 22-year-old. OGJ non-relaxation, despite adequate peristaltic response is seen in 4A, while normal relaxation responses are seen in association with peristalsis (B) or fragmented peristalsis (C).

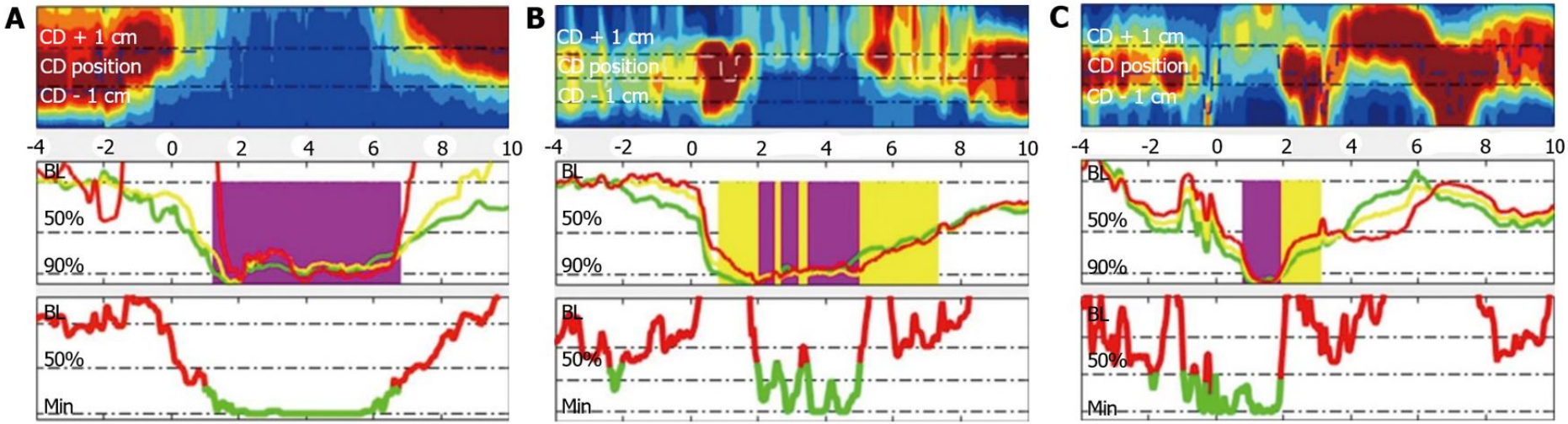


Figure 7.5 Examples of bolus flow time calculation. Both flow and pressure criteria need to be satisfied for bolus flow (purple) (5A). If only the impedance criteria are met, but flow is interrupted by an increase in pressure due to vascular (5B) or crural contraction (5C), no flow is measured (yellow).

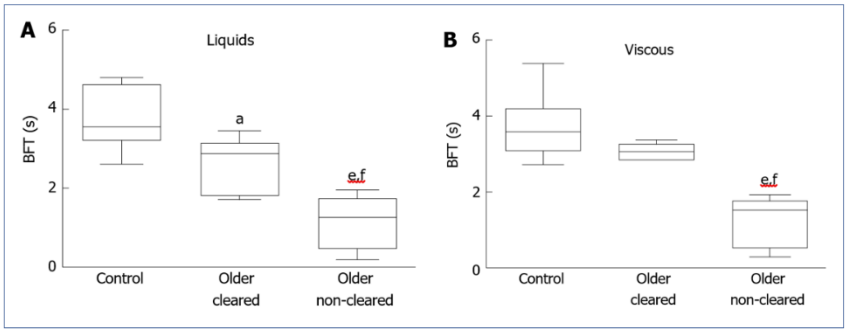


Figure 76. Reduced bolus flow time s in asymptomatic older subjects during liquid and viscous swallows by impedance criteria, when compared to young controls (control). a $P < 0.05$, e $P < 0.001$ vs control; f $P < 0.001$ vs older cleared. BFT: Bolus flow time.

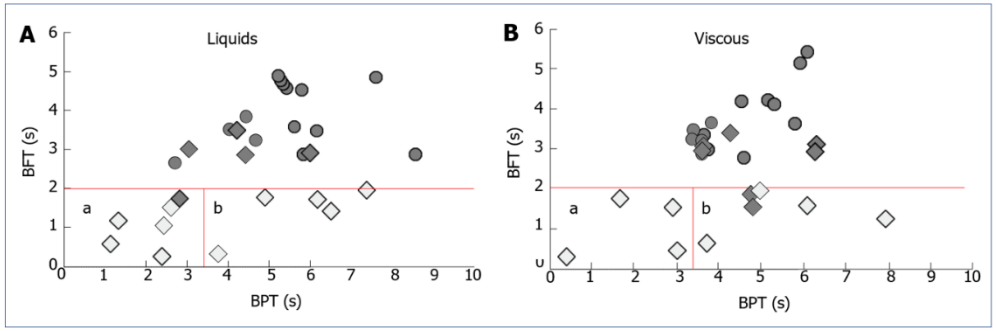


Figure 7.7 Bolus flow time vs bolus presence time in older subjects with (filled diamonds) and without (open diamonds) bolus clearance and controls (filled circles) during liquid (7A) and viscous (7B) swallows. All older subjects with failed bolus clearance had a reduced BFT (5th percentile control BFT and BPT shown in red). BFT/BPT matrix can be used to differentiate individuals with failed clearance into those with equivalent reduced BPT (a), indicative of ineffective esophageal motility, and those with increased BPT (b), indicative of bolus retention above the esophagogastric junction due to increased flow resistance. BFT: Bolus flow time; BPT: Bolus presence time.

7.4 Discussion

This is the first study to report the influence of aging on several novel metrics assessing oesophagogastric junction function. OGJ barrier function is assessed through the OGJ-CI, while swallow-induced OGJ relaxation is assessed through the IRP4 and associated bolus passage through bolus flow time (BFT). Our study shows evidence of (1) unchanged OGJ barrier function as measured via OGJ-CI; (2) reduced swallow- induced OGJ relaxation, which also increases the “total” OGJ-CI, which is measured during swallowing; and (3) reduced bolus flow time during both liquid and viscous swallowing, in aging. There is no evidence to support OGJ barrier dysfunction as a significant pathogenic factor in the increased incidence of gastro esophageal reflux disease reported in aging [26]. However, reduced OGJ relaxation in concert with greater intragastric pressure and reduced distal esophageal bolus clearance implies potential prolonged retention of gastric refluxate in the distal esophagus, potentially leading to greater mucosal damage by the refluxate. The unproven hypothesis is that reduced OGJ relaxation is an obstructive antegrade barrier once contents have refluxed. Impedance pH studies were not undertaken in these healthy, asymptomatic individuals but such studies would be of interest in this cohort. Due to an increased sensory threshold, reflux symptoms may not be perceived by the aging reflux patient [26,27]. A low threshold should be maintained for further clinical assessment (e.g., via endoscopy) of upper gastrointestinal symptoms in older subjects and a recognition that older subjects do not always present with typical symptoms.

Older patients with gastroesophageal reflux disease often present with atypical symptoms, including dysphagia [28], have an increased prevalence of erosive reflux disease [19,28] and also have associated motility disturbances [29]. Our findings that esophageal barrier function, as measured through OGJ-CI, is unchanged in older individuals have important implications for the assessment of aged patients with gastroesophageal reflux disease or undergoing high-resolution manometry for other indications. Whilst the resting OGJ-CI is congruent with “total” OGJ-CI in young subjects, this is not the case in subjects aged greater than eighty years. This is because decreased swallow-induced LES relaxation in these older subjects would increase

the measured OGJ-CI during swallowing (“total” OGJ-CI). “Total” OGJ-CI would not be a reliable measurement of OGJ barrier function in older subjects and should not be clinically used to determine such function.

Our findings of a similar OGJ-CI in older subjects and younger controls are in keeping with those of Bardan et al. [30] who showed similar LES resting pressure in healthy older volunteers as compared to younger in a supine posture. Other studies have shown either higher [16] or lower [17] resting pressures in aged individuals. In terms of the functional consequences of impaired OGJ barrier function, Lee et al. [26] described increased distal esophageal acid exposure related to dysmotility and reduced acid clearance in older subjects with reflux disease. Their study also showed increased esophageal abdominal length [26]. Other studies have likewise shown increased prevalence of hiatus hernia in aging [28]. Our study in older subjects studied in a sitting posture did not find an increased prevalence of hiatus hernia as assessed by OGJ “subtypes”. Our study did, however, find decreased swallow-induced relaxation, discussed further below. In this context, care needs to be taken in exactly how the OGJ-CI is calculated, i.e., whether at rest or during swallowing, with only values at rest being clinically relevant in subjects over eighty, as discussed above.

Our findings demonstrating reduced swallow- induced OGJ relaxation in healthy aging, is consistent with a previous study by Besanko et al. [18], which showed decreased swallow-induced relaxation, as measured through the IRP4, in healthy older adults over eighty years. Likewise, Jung et al. [31] also showed a significant correlation of IRP4 with age and aging. The finding of decreased swallow-induced OGJ relaxation with aging is consistent with degeneration of myenteric lower motor neurons. Degeneration of such neurons have previously been demonstrated in aging animals [32] and humans [33]. Myenteric neurons and in particular cholinergic neurons [34], seem to represent a vulnerable subpopulation when compared to neuronal cells elsewhere in the body [35]. Furthermore, our findings indicating more proximal bolus retention [15] also implies decreased distal esophageal distention [36], decreasing the stimulus for nitrinergic distention based OGJ relaxation [37]. Lastly, aged subjects have decreased esophageal sensory function and by implication a lesser perception

of the stimulus for bolus/distention- based OGJ relaxation. The clinical implications of these findings are the potential for prolonged retention of refluxed contents, leading to the observed increase in erosive reflux disease in this population, but also longer esophageal retention of swallowed contents leading to a higher prevalence of “pill” esophagitis; and increased prevalence of esophageal dysphagia symptoms (or asymptomatic swallowing dysfunction) in the aging population. Esophageal bolus transit is reduced in this population [15] and thus an additional factor of decreased swallow-induced LES relaxation may change borderline bolus transport into clinically relevant dysphagia.

In our study, bolus flow time (BFT) at the OGJ was markedly reduced in older subjects when compared to controls. Further analyses revealed BFT was most markedly reduced in those individuals with impaired esophageal bolus clearance (Figure 7.6). Reduced OGJ bolus flow time has previously been shown in association with ineffective esophageal motility [14]. By adding bolus presence time (BPT) at the most distal impedance segments above the OGJ, we can draft a matrix (Figure 7) representing the main causes of reduced BFT, namely (1) reduced bolus clearance (reduction in both BPT and BFT) and (2) increased OGJ flow resistance, similarly to that in achalasia [13] (reduced BFT with increase in BPT). Our previous data suggested reduced overall esophageal bolus clearance [15] in older volunteers. Further assessment of the esophageal bolus clearance through a BFT/BPT matrix revealed an equivalent proportion of failed clearance due to ineffective esophageal motility and increased OGJ flow resistance, revealing that both these factors play a role in reduced esophageal bolus clearance in older individuals and as described above may lead to clinically relevant dysphagia.

Our study has some limitations. We did not record pH-metry, in order to assess the implications of potential changes in OGJ barrier function as measured in our study, as we could not justify acquiring pH-metry in asymptomatic volunteers. A specific assessment of OGJ metrics in aged individuals undergoing pH studies would be of value. Subjects were excluded if they reported reflux related symptoms or were on anti-reflux medications (other than occasional over the counter medications). We cannot exclude having inadvertently

included asymptomatic individuals with reflux disease in our study. Furthermore, transient lower esophageal sphincter relaxations (TLESR's) were not assessed during our study. Our study was not designed to assess TLESR's, but a study of TLESR activity in aging would be of great value as to our knowledge, TLESR's have never been specifically assessed in the aged population.

Our study showed evidence of similar OGJ barrier function at rest, but not during swallowing; reduced swallow-induced relaxation and markedly reduced bolus flow time (BFT) at the OGJ in older individuals. The use of a BPT/BFT matrix allowed us to determine different causes for reduced BFT in aging, indicating equivalent numbers being due to failed bolus clearance and increased OGJ flow resistance. Our study has important implications for better understanding mechanisms of failed bolus clearance in older individuals and in guiding investigation in older subjects with gastroesophageal reflux disease, where non-clearance of refluxate predisposes older subjects to increases in distal esophageal acid exposure, potentially explaining the increased prevalence of severe reflux esophagitis in older GERD patients [19]. Our study also implies the OGJ, in addition to the oropharynx and distal esophagus, should be a focus during investigation and may be a potential therapeutic target (e.g., for dilatation) in aged patients with dysphagia.

Chapter 8 Longitudinal Change in Pharyngeal & Oesophageal High-Resolution Manometry with Impedance (HRM-I) in Asymptomatic Older Persons

Abstract

Background: Studies of asymptomatic older persons have demonstrated reduced upper oesophageal sphincter (UOS) relaxation and increased hypopharyngeal contractility, compared to younger cohorts, while in the oesophagus, contractility and lower oesophageal sphincter (LOS) relaxation was reduced. There are no published studies of changes across time intervals (interval change) in high-resolution manometry with impedance (HRM-I) metrics in asymptomatic healthy volunteers. The aim of this study was to measure interval change in pharyngeal and oesophageal HRM-I in asymptomatic young and older persons.

Methods: Paired pharyngeal high-resolution manometry impedance data from younger (21-79 years of age); and older (80 years of age and older) healthy volunteers were selected from studies performed at intervals no less than one year apart (median 4-6 years). 10ml liquid (international dysphagia diet standardisation initiative – IDDSI level 0) and viscous (IDDSI level 4) boluses, averaged per participant, were analysed to determine pharyngo-UOS and oesophago-LOS metrics. A repeated measures mixed model ANOVA with post-hoc testing was conducted using time and groups (younger/older) as variables. A P-value of < 0.05 was considered significant.

Results: Eighteen younger (mean age 54±18 years) and ten older participants (mean age 84±4 years) were included. Velopharyngeal contractility was significantly increased in the older group during their repeat studies ($P < 0.01$). No other contractile integrals changed over time but there was a reduction in hypopharyngeal peak pressure over time within the older group ($P < 0.05$). The extent of UOS opening distension decreased across timepoints in both groups ($P < 0.05$). UOS relaxation reduced (higher UOS IRP) in the older group compared to controls ($P < 0.05$) and baseline studies ($P < 0.01$). The composite measure swallow risk index (SRI) increased in the older group compared to younger and over time. On repeat measurement, half of the older participants had reached a threshold associated with

deglutitive aspiration risk (SRI>15). Oesophageal analysis showed that LOS relaxation was reduced in the older, compared to the younger group and over time ($P < 0.05$). Oesophageal contractility during viscous swallowing reduced in the older group over time ($P < 0.05$). Oesophageal bolus retention increased in the older group during viscous swallowing compared to the younger group and over time ($P < 0.05$)

Conclusion: Biomechanical abnormalities in keeping with UOS and LOS flow restriction were observed in older persons over time.

8.1 Introduction

Swallowing dysfunction, with or without symptoms, becomes more prevalent with advancing age (Cook 2009). Many older persons accept a degree of dysphagia as a normal part of the ageing process and would disregard it as relevant to their overall wellbeing (Smithard 2016). In cases where swallowing biomechanics have been objectively measured in older individuals, abnormalities in oropharyngeal function were demonstrated even when not self-reported (Molfenter et al. 2018, Molfenter et al. 2018 no. 2, Mancopes et al. 2021). In the oesophagus, radiological and manometric changes encompassing reduced primary peristalsis, uncoordinated contractions, delayed barium clearance and oesophageal dilatation have also been described as presbyesophagus (Soergel et al. 1964, Zobralske et al. 1964)

The current thinking is that swallowing dysfunction in older persons mostly relates to abnormal oropharyngeal mechanisms (Cook 2009), while oesophageal dysfunction in older persons is thought to result from intercurrent illnesses such as diabetes mellitus or potentially even undiagnosed gastroesophageal reflux disease (Tack & VanTrappen 1997, DeVault 2002). Neurodegeneration of excitatory and inhibitory components of the myenteric plexus have been demonstrated in older animals and humans, which suggest some changes may relate to ageing per se (Meciano Filho et al. 1995, Phillips et al. 2003, Kim et al. 2017).

This thesis, as well as past pharyngeal manometric studies in asymptomatic older persons have demonstrated reduced UOS resting pressure, relaxation and increased pharyngeal contractility, when compared to young controls (Kern et al. 1999, Nativ-Zeltzer et al. 2016). Oesophageal studies have shown reduced distal oesophageal contractility and LOS relaxation, when compared to younger controls (Besanko et al. 2014, Jung et al. 2015, Cock et al. 2016, Cock et al. 2017, Djinbachian et al. 2021)

In this research program, changes consistent with the existing literature, as related to the UOS, were demonstrated in the oropharynx (Chapter 5), while oesophageal and oesophagogastric junction studies (Chapters 6 and 7) demonstrated, in addition to previously observed changes, markedly reduced bolus clearance, particularly of increased consistencies, in asymptomatic older persons over the age of eighty years.

To date, no studies could be identified that evaluate longitudinal changes in swallowing biomechanics measured using high-resolution manometry with impedance (HRM-I) in healthy volunteers. The paucity of published data on this topic is understandable given the challenges inherent in conducting repeat studies, in healthy volunteers, with sufficient fidelity to detect changes in swallowing function of relatively short time frames.

In order to address this gap, I evaluated repeat high-resolution manometry with impedance studies, performed >12 months apart in asymptomatic healthy volunteers. The participants were divided into two groups based on their age at the time of original investigation: controls aged 21-79 years and older participants aged ≥ 80 years. The study aims were:

1. To determine between group (older vs younger) effects on HRM-I core metrics, and
2. To determine changes that occur between baseline (study 1) and follow up (study 2) studies, occurring more than 12 months apart.

The study hypothesis was that biomechanically measurable changes indicating reduced UOS relaxation, increased pharyngeal contractility, reduced oesophago-gastric junction relaxation,

reduced distal oesophageal contractility and bolus clearance would occur in older, but not younger participants and that these changes would worsen within the older group between baseline and follow-up studies.

8.2 Methods

8.2.1 Participant selection

Participants were selected from asymptomatic healthy volunteers who had undergone repeat high-resolution manometry with impedance assessments of pharyngeal and oesophageal function no less than 12 months apart. The assessments may have been part of the same or different protocols, provided identical equipment and at minimum 3 repeats of boluses of 10ml liquid (IDDSI Level 0) and viscous (IDDSI Level 4) were used. All these studies included multiple additional bolus volumes and consistencies, which were not analysed for this study.

8.2.2 Groups and inclusion/exclusion criteria

Participants were grouped by age at study onset (baseline) as follows:

Younger: Asymptomatic healthy volunteers aged between 21 and 79 years of age.

Older: Asymptomatic healthy volunteers aged 80 years of age and above.

The selection of the cut-off age of 80 years was made based on past observations of abnormal pharyngeal and oesophageal function above this age by others (Andrews et al. 2008, Andrews et al. 2009, Omari et al. 2014) and within this research program (see Chapters 5, 6 and 7).

Studies were selected in pairs consisting of a baseline study (study 1) and a follow up study (study 2) with the second study being the latest study undertaken per individual meeting inclusion criteria, as below.

Inclusion criteria:

1. Aged above 21 years of age (adult studies),
2. Asymptomatic of dysphagia and reflux symptoms by validated questionnaires,
3. Written, informed consent for all studies,

4. Paired manometry studies using similar equipment and boluses, more than 12 months apart.

Exclusion criteria:

1. Failure to obtain or withdrawal of informed consent,
2. Upper gastrointestinal tract surgery other than cholecystectomy,
3. Uncontrolled diabetes mellitus of other medical conditions known to affect oropharyngeal or oesophageal motility (e.g., stroke, scleroderma),
4. Chronically on medications affecting oesophageal function e.g., opioids, tricyclic antidepressants, antipsychotics, etc. or permanently on PPI therapy for the treatment of suspected gastroesophageal reflux disease,
5. Pregnancy or suspected pregnancy (related to controls)

8.2.3 Participant study consent

Ethics approvals were obtained for all studies from the Southern Adelaide Human Research Ethics Committee, including the original study and amendments for 403.10, 215.13, 444.14, 188.17, and 76.17. All participants signed informed consent for each occasion when manometry was undertaken.

8.2.4 Manometry studies

Manometry studies were conducted as per the description in Chapter 4 (Ch 4, p 106).

8.2.5 Statistical methods and data analysis

A repeated measures mixed model ANOVA with Greenhouse-Geiser correction was conducted in SPSS version 27.0. Prior to settling on the final model, three different age groups were included in the model but when no differences were demonstrated between the two younger age cohorts (20-59 years and 60-79 years) for any of the HRM-I metrics, these “younger” groups were combined as “controls” for the older group (80 years and above), leaving two groups: controls (20-79 years of age) and older (80 plus). Gender was also

included in the initial model but when no gender differences were demonstrated, was excluded for subsequent analyses.

Analyses were done for individual manometric variables (“metrics”) to test within group effects over time with time and group as factors. The time between the earliest and latest study per individual was used to satisfy conditions for sphericity to ensure validity of the statistical model used. Univariate analyses with post-hoc testing and Bonferroni correction were conducted for each individual study to determine between group differences for each individual variable per study. Groups were then split, and repeated measures ANOVA conducted with Greenhouse-Geiser correction and post-hoc Bonferroni correction in order to determine within group effects for each variable comparing the initial and the later study.

Descriptive statistics, additional between group comparisons using t-tests or Fisher’s exact tests for proportional comparisons and graphing of figures were conducted using Graphpad Prism version 9.3.1 (Graphpad Software, San Diego, Ca, USA). Within group paired analyses determining the mean of differences were also performed. For all statistical tests a P-value < 0.05 was considered significant.

8.3 Results

8.3.1 Participants

Participant characteristics are included as Table 8.1. The mean age of younger participants at the start of the study was 54±18 years (range 21-73 years of age), which is significantly younger than the older cohort aged 84±4 years (range 80-89 years of age) (P < 0.001). More male participants were recruited but between gender difference did not reach statistical significance. Including gender in a mixed model analysis did not change the results (not shown). The median intervals between studies 1 and 2 in the younger and older groups were 6 and 4 years, respectively.

Table 8.1 Characteristics of Participants

	Younger	Older	P-value
Number (n =)	18	10	
Mean age ± st dev (range) at Study 1	54±18 (21-73) yrs	84±4 (80-89) yrs	< 0.001
Mean age ± st dev (range) at Study 2	59±18 (24-79) yrs	89±4 (85-94) yrs	< 0.001
Gender (M/F)	8/10	8/2	0.05
Median Interval between studies (range)	6 (1-7) yrs	4 (1-5) yrs	0.06

8.3.2 Pharyngeal swallow function metrics

The results of pharyngeal swallow function metrics for 10ml liquid boluses are included as Table 8.2 and 8.3. For measures of pharyngeal contractility, measured as contractile integrals, there were no differences between groups. The velopharyngeal contractile integral (VCI) increased between studies 1 and 2 in the older group (84±19 vs. 117±19 mmHg.s.cm; P < 0.01), with a trend towards an increase in the younger group (Table 8.2). In contrast with what was expected, there was a strong trend towards a *decrease* in mean hypopharyngeal peak pressures, analogous to the hypopharyngeal pressures measured by Kern et al. (Kern et al. 1999) between studies 1 and 2 in the older group (157±26 vs. 115±16mmHg; P = 0.05).

Table 8.2 Pharyngeal Metrics in Controls and Older Healthy Volunteers

	Younger		Older	
	Study1 (21-73 yrs)	**Study 2 (24-79 yrs)**	**Study 1 (80-89 yrs)**	**Study 2 (85-94 yrs)**
Pharyngeal Contractility				
PhCI (mmHg.s.cm)	267±28	299±33	253±35	283±39
VCI (mmHg.s.cm)	64±6	86±10	84±19	117±19$^{\#\#}$
MCI (mmHg.s.cm)	130±15	153±20	97±15	116±20
HPCI (mmHg.s.cm)	52±5	54±5	62±7	47±5
Upper Esophageal Sphincter				
UOS IRP (mmHg)	0.5±0.8	-1.8±1.7	4.2±1.6*	6.7±1.8**,$^{\#}$
IBP (mmHg)	7.5±1.5	8.0±1.6	10.4±4.1	14.1±4.4
UOS RT (msec)	584±23	548±19	579±31	565±41
UOS Max Adm (mS)	9.2±0.6	5.6±0.2$^{\#\#\#}$	6.5±0.4**	5.2±0.4$^{\#}$
Swallow Risk Index median [25th P; 75th P]	2[0;4]	2[1;5]	2[1;7]	9[3;20]*,$^{\#}$
Between group Study 1 vs.1 or 2 vs.2(Unpaired t-test): * P < 0.05; ** P < 0.01; *** P < 0.001				
Within group (Paired t-test or Wilcoxin rank sum test): $^{\#}$ P < 0.05; $^{\#\#}$ P < 0.01; $^{\#\#\#}$ P < 0.001; *Ave 5 swallows*				

There was a reduction in UOS distension (UOS maximum admittance) when comparing the initial studies (study 1) between younger and older participants (Table 8.2; P < 0.01) and within both younger (Table 8.2; P < 0.001) and older groups (Table 8.2; P < 0.05) between studies 1 and 2.

UOS IRP increased between younger and older groups for study 1 (0.5±0.8 vs. 4.2±1.6mmHg; P < 0.05) and 2 (-1.8±1.7 vs. 6.7±1.8mmHg; P < 0.01). UOS IRP also further increased between studies 1 and 2 in the older group (4.2±1.6mmHg vs. 6.7±1.8mmHg; P < 0.05) (Figure 8.1).

The SRI increased for study 2 in older participants when compared to both the younger group (studies 1 and 2) (P < 0.01) and study 1 in older participants (P < 0.05) (Figure 8.2). As per Figure 8.3, pairwise comparisons of SRI and all components comprising this metric revealed that several metrics in concert resulted in an increased SRI in older participants: increased hypopharyngeal intrabolus pressures, decreased hypopharyngeal mean peak pressures and reduced timing between hypopharyngeal distension and contraction.

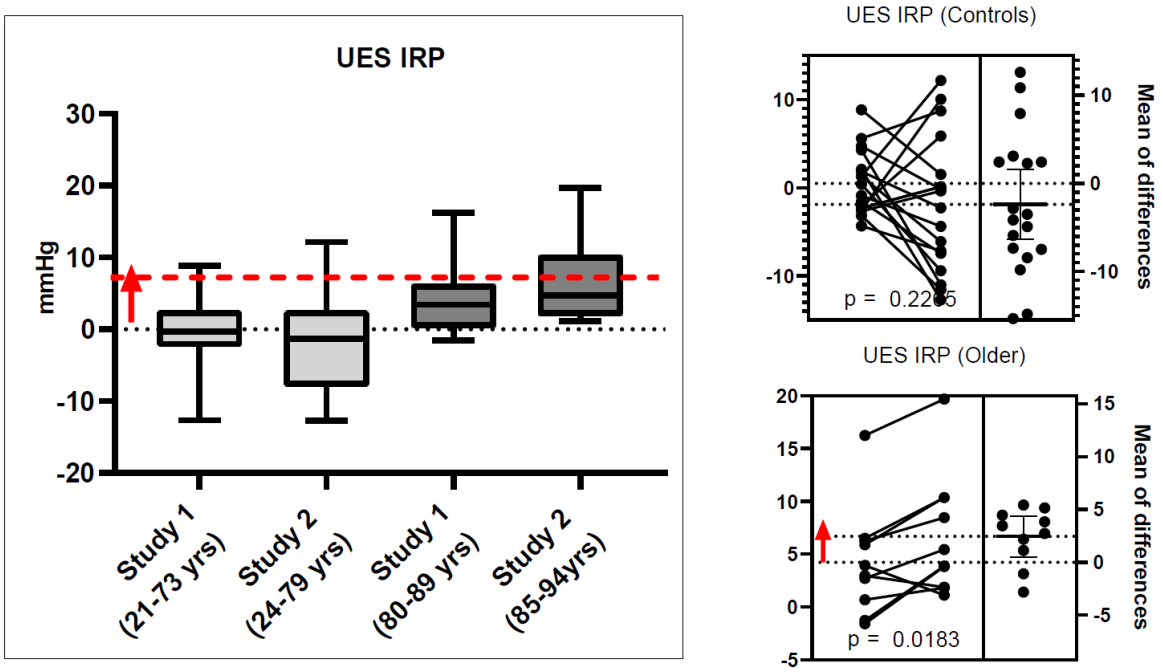


Figure 8.1. Upper oesophageal sphincter integrated relaxation pressure (UOS IRP) increased with increasing age and in the older group, aged 80-89 years at study onset, further increased between initial and follow-up studies conducted a median of 4 years later. The upper limit of normal is displayed (broken red line).

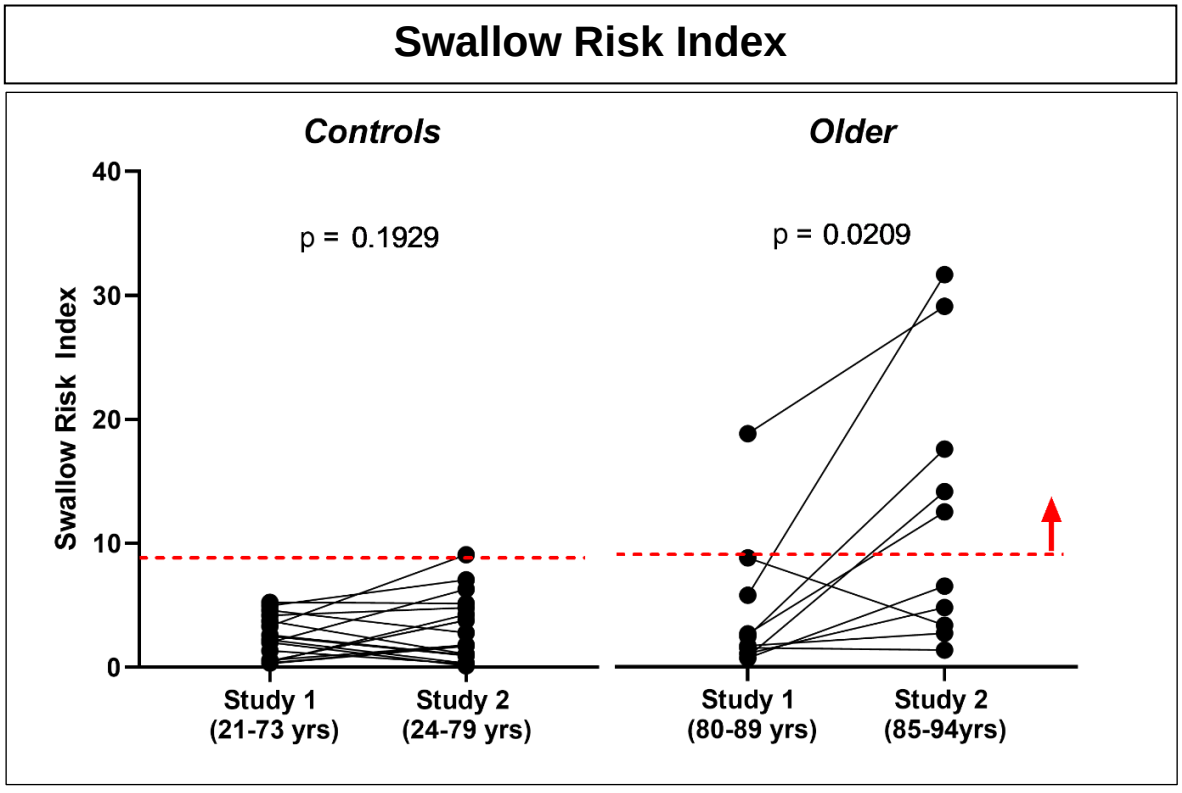


Figure 8.2. Swallow Risk Index (SRI) in asymptomatic younger and older participants showing a significant increase in older subjects to above the threshold previously show to be associated with deglutitive pulmonary aspiration (broken red line)(Omari 2011, Bayona et al 2022) This increase in asymptomatic older participants is significant when compared to younger (P = 0.01; Fisher's exact test).

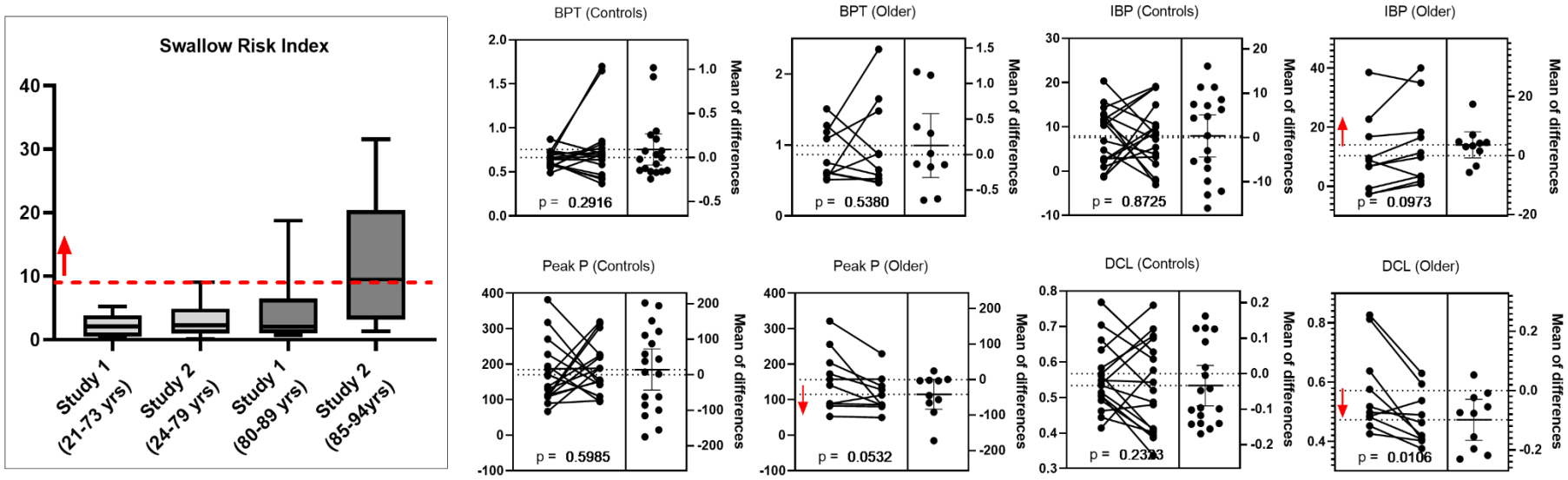


Figure 8.3. Swallow risk index (SRI) for all studies, showing an increase with older age. Pairwise data and mean of differences shown on the right-hand side. SRI increase in the older group is driven by higher IBP and reduced time from distension to contraction and hypopharyngeal peak pressures. Increased risk of pulmonary aspiration occurs above SRI of 9 (Bayona et al. 2022), indicated by the broken red line.

Table 8.3 Repeated Measures ANOVA for pharyngo-UOS (study 1 vs study 2)

	Within Subjects				Between Subjects	
	Time	**P-value**	**Time x Group**	**P-value**	**Groups**	**P-value**
Pharyngeal Contractility						
PhCI (mmHg.s.cm)	F = 0.878	0.36	F = 0.005	0.94	F = 0.203	0.66
VCI (mmHg.s.cm)	↑F = 10.332	**0.003**	F = 0.427	0.52	F = 2.846	0.10
MCI (mmHg.s.cm)	F = 0.639	0.43	F = 0.191	0.67	F = 1.904	0.18
HPCI (mmHg.s.cm)	↓F = 4.715	**0.04**	F = 0.072	0.79	F = 0.124	0.73
Upper Esophageal Sphincter						
UOS IRP (mmHg)	F= 0.799	0.38	F = 0.380	0.40	↑F = 8.085	**0.009**
IBP (mmHg)	F = 1.257	0.27	F = 0.228	0.63	F = 2.527	0.12
UOS RT (msec)	F = 1.744	0.19	F = 0.302	0.59	F = 0.030	0.87
UOS Max Adm (mS)	↓F = 25.473	**<0.001**	↓F = 6.724	**0.02**	↓F = 3.190	**0.08**
Swallow Risk Index	F = 2.102	0.16	F = 0.914	0.35	↑12.753	**0.001**
Average of five swallows per individual						

8.3.3 Oesophageal Pressure Topography

Results of the Chicago Classification metrics (oesophageal pressure topography) are included as Table 8.4.

Table 8.4 Chicago Classification Metrics

	Younger		**Older**	
	Study1 (21-73 yrs)	**Study 2 (24-79 yrs)**	**Study 1 (80-89 yrs)**	**Study 2 (85-94 yrs)**
Liquids (IDSSI 0)				
IRP4 (mmHg)	8±1	9±2	9±1	17±5*,#
DCI (mmHg.s.cm)	1236±263	1123±264	1102±326	529±213
DL (sec)	6.8±0.4	6.9±0.4	9.1±1.0*	8.3±0.8
PB (cm)	1.3±0.6	2.0±0.5	3.9±1.6*	5.3±2.1
Viscous (IDSSI 4)				
IRP4 (mmHg)	8±3	9±2	9±3	20±4*,#
DCI (mmHg.s.cm)	1272±515	829±245	1122±406	592±225#
DL (sec)	7.1±0.3	7.3±0.4	8.5±0.8	7.8±0.8
PB (cm)	1.6±0.8	1.7±0.6	3.5±1.3	3.3±1.1
Mean ± standard error of measurement; Average of five swallows per individual. **P < 0.05 vs. younger (unpaired t-test); # P < 0.05 vs. study 1 (paired t-test)*				

Integrated relaxation pressures increased in the older group during study 2 compared to both the younger group and their own baseline for both liquid and viscous swallows. Distal latencies were increased in the older group compared to younger for liquids study 1 only and lengths of peristaltic breaks were also increased in the older group during liquid swallows (study 1).

During swallows of thicker consistency (Viscous; IDSSI 4), distal contractile integral decreased in the older group between studies 1 and 2.

8.3.4 Oesophageal Pressure-Flow Analysis

Results of oesophageal pressure flow metrics are included are included as Table 8.5.

Table 8.5 Oesophageal Pressure-Flow Metrics

	Younger		Older	
	Study1 (21-73 yrs)	**Study 2 (24-79 yrs)**	**Study 1 (80-89 yrs)**	**Study 2 (85-94 yrs)**
Liquids (IDSSI 0)				
PFI	18±5	38±11	9±2	13±4
IR*	0.27±0.03	0.31±0.03	0.34±0.06	0.40±0.05
DPA (mmHg)	1.0±0.5	-1.8±1.1	1.4±0.8	5.0±1.2***,#
DPCT (mmHg)	3.8±0.9	0.2±1.0	2.4±0.8	8.8±2.1***,#
DPE (mmHg)	9.4±1.3	11.1±1.3	10.6±2.1	21±3.3**,#
RP (mmHg.s)	3.8±0.5	9.3±2.1#	3.2±0.9	2.9±0.6**
SDL (sec)	3.5±0.5	4.4±0.5	5.3±0.9	4.6±1.1
DCL (sec)	3.3±0.3	2.6±0.3	3.8±0.2	3.9±0.4
BFT	4.0±0.4	3.5±0.3	4.0±1.3	3.1±0.8
Viscous (IDDSI 4)				
PFI	54±19	78±24	60±18	67±23
IR	0.37±0.02	0.42±0.03	0.51±0.04	0.60±0.05**,#
DPA (mmHg)	3.0±1.5	0.3±1.1	2.8±1.3	0.1±0.9
DPCT (mmHg)	6.5±1.6	3.6±1.5	4.9±1.2	7.2±1.6
DPE (mmHg)	12.3±2.8	14.1±2.2	16.8±2.0	24.8±3.5*
RP (mmHg.s)	6.0±1.2	8.9±3.3	7.1±2.4	3.3±0.7
SDL (sec)	4.8±0.5	5.6±0.4	6.0±0.7	5.7±0.4
DCL (sec)	2.1±0.3	1.8±0.2	2.6±0.5	2.8±0.5
BFT	3.5±0.6	2.9±0.4	2.6±0.5	3.8±0.7

Mean ± standard error of measurement. Average of five swallows per individual.
**P < 0.05, ** P < 0.01, *** P < 0.001 vs. younger (unpaired t-test);*
 # P < 0.05 vs. study 1 (paired t-test)

Distension pressures throughout the oesophagus increased in the older group when compared to younger ($P < 0.01$) and when comparing study 1 and 2 in the older group, during liquid swallows ($P < 0.05$). The rate of pressure increase, above the EGJ (ramp pressure), also increased compared to younger ($P < 0.01$). During viscous swallowing only the distension emptying pressure increased in the older group when comparing studies 1 and 2 ($P < 0.05$).

The impedance ratio, a measure of oesophageal bolus retention, increased in the older, compared to younger group and the older group (P <0.01) and between studies 1 and 2 (P < 0.05) (Table 8.5, Figure 8.4)

8.3.5 Oesophagogastric Junction (OGJ/EGJ) function

Results of OGJ function are included as Table 8.6

Table 8.6 Oesophagogastric-junction Metrics

	Younger		**Older**	
	Study1 (21-73 yrs)	**Study 2 (24-79 yrs)**	**Study 1 (80-89 yrs)**	**Study 2 (85-94 yrs)**
IRP4 (mmHg) liquids	8±1	9±2	9±1	17±5*,#
IRP4 (mmHg) viscous	8±3	9±2	9±3	20±4*,#
OGJ-CI (mmHg.s)	45±10	49±10	61±6	55±5
OGJ-RP (mmHg)	28±6	26±5	32±4	42±4*,#
Mean ± standard error of measurement. *Average of five swallows per individual.* *P < 0.05, ** P < 0.01, *** P < 0.001 vs. younger (unpaired t-test); # P < 0.05 vs. study 1 (paired t-test)				

Figure 8.5 shows examples of OGJ resting and relaxation pressures and IRP4.

IRP4 was increased, meaning LES relaxation reduced, in the follow up studies (study 2) in the older group, compared to both the younger group (P < 0.05) and their own baseline studies (study 1 in older; P < 0.05) for both liquid and viscous swallows.

Figure 8.5F shows that there was a substantial overlap in the EGJ contractile integral metric between the younger and older groups explaining why this metric is not different even when resting pressures were slightly higher in the upright posture in the older group compared to the younger group and their own baseline P < 0.05; Fig 98.5H).

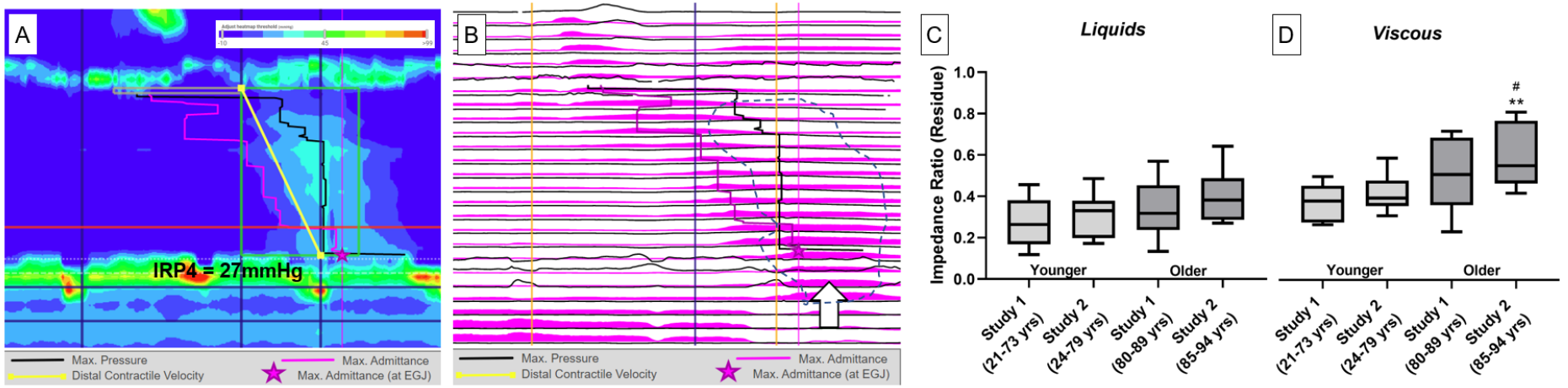


Figure 8.4 Increase in impedance ratio (IR) in older persons. IR (residue) in an example swallow in a 85 year old healthy volunteer (8.5A) shown arrow in line plot (8.5B). With increases between studies 1 and 2 shown for younger and older groups during liquid (8.5C) and viscous (8.5D) swallowing.

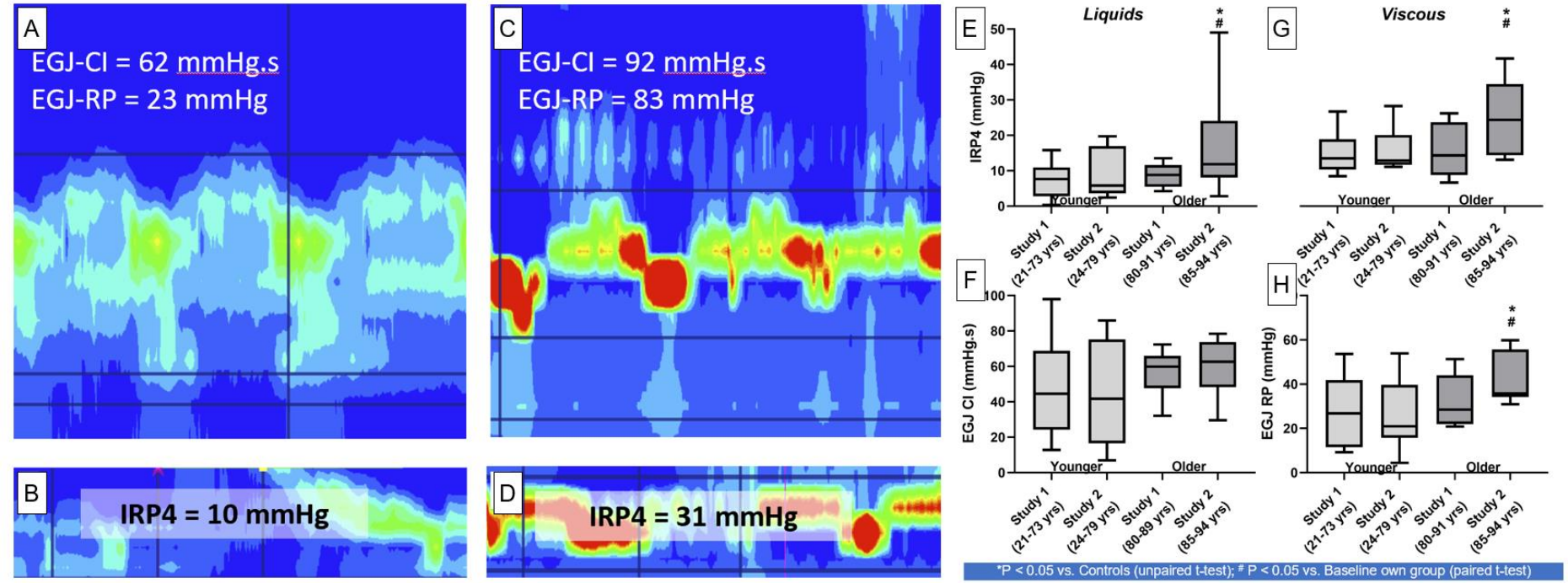


Figure 8.4 Examples of OGJ (EGJ) measurements in a 64-year-old younger female (8.5A/B) and an 85-year-old older male (8.5C/D). These examples demonstrate OGJ resting (8.5 A/C) and relaxation (8.5 B/D).

8.4 Discussion

This study compares pharyngeal contractility, UOS metrics, oesophageal pressure topography, pressure-flow analyses and oesophagogastric junction outflow in younger and older healthy volunteers in HRM-I studies performed using identical equipment 4-6 years apart.

8.4.1 Pharyngo-UOS Changes in Older Persons over Time

Reduced UOS relaxation (increased UOS-IRP) was shown in the older group compared to both the younger group and their own baseline. Reduced UOS relaxation had previously been described when comparing older and younger healthy volunteers (Nativ-Zeltzer et al. 2016, Omari et al. 2022). This study expanded on that finding by demonstrating not only an increase in UOS-IRP between older and younger individuals, but also *within* the older group, in keeping with progressive reduction in UOS relaxation in older persons beyond eighty years of age. A novel related finding was the reduced UOS bolus-based distension (UOS maximum admittance) observed in both groups at their follow up studies, and when comparing study 1 in the older and younger groups. Observed changes would be in keeping with reduced UOS distensibility due to increased fibrosis in the cricopharyngeus previously described in older persons (Cook et al. 1992, Leonard et al. 2004).

Few changes were observed in pharyngeal contractile integrals overall and the previously reported increase in hypopharyngeal contractility (Kern et al. 1999, Nativ-Zeltzer et al. 2016) was not observed in this study. In fact, in contrast with previous findings, this study showed that hypopharyngeal peak contractility reduced in the older group between their baseline and follow-up studies. While a past hypothesis was that increased hypopharyngeal contractility compensates for increased UOS restriction (Shaker et al. 1993, Kern et al. 1999, Nativ-Zeltzer et al. 2016), this study suggests compensatory mechanisms may fail in those older than eighty-five years of age. If one considers reduced UOS relaxation and opening in concert with

reduced hypopharyngeal pharyngeal contractility, there would be a lesser increase in hypopharyngeal intrabolus pressures (due to decreased driving force) (Szczesniak et al. 2018), meaning hypopharyngeal IBP would be a less reliable predictor of UOS dysfunction in older persons, an important observation relating to pressure-only (sans impedance) pharyngo-UOS manometry in older persons. By implication, pressure only HRM may be unreliable in identifying or fully understanding the implications of UOS outflow restriction in older persons.

Another important novel observation was an increase in SRI the older group, compared both to the younger participants and their own baseline. While Omari et al. (Omari et al. 2014) had previously demonstrated an increased SRI in healthy older persons, this study demonstrates a further increase within individuals older than eighty-five years of age. Specifically, half the participants in this chapter had swallowing biomechanics indicative of increased aspiration risk (Fig 8.2) and participants were aged 85-94 years at the time of the second study. These findings are congruent with observations suggesting aspiration may occur in community dwelling older persons (Serra-Prat 2012). Further analyses revealed numerical trends towards increased intrabolus pressures, decreased hypopharyngeal peak pressures and increased time from distention to contraction as primary drivers of the change in SRI (Fig 8.3).

Overall, pharyngo-UOS changes are in keeping with a greater extent of flow restriction at the UOS (manifest as increased IBP), potentially failing compensatory mechanisms (reduced hypopharyngeal peak pressures) and increased neurosensory feedback to further compensate (shortening contractile interval).

8.4.2 Oesophageal Changes in Older Persons over Time

Reduced LOS relaxation (increased IRP4) was shown in the older group compared to both the younger group and their own baseline. This finding is in keeping with past observations in older healthy volunteers (Besanko et al. 2014), including in this research program (Chapter 6). What is interesting and novel, is that IRP4 increased more in the older cohort in a relatively

short time span between studies 1 and 2 (mean 4 years). It is postulated that the observed change in IRP4 relates to neurodegenerative changes in the peripheral component of LES relaxation (Kim et al. 2017), in concert with mechanical changes (reduced elasticity/increased fibrosis) at the OGJ in older persons. OGJ resting pressures were also increased in older persons compared with younger and their own baseline. It is of interest to note that these changes were not observed for the OGJ-CI, which has a wide variability between individuals.

To overcome increased flow resistance at the OGJ (evidenced above), contractility and/or distension pressures would need to increase to maintain the pressure differential needed for flow to occur at the OGJ (Nicosia and Brasseur 2002, Quader et al. 2017, Triggs et al. 2019). An increase in distension pressures was observed in the older, as compared to the younger group. This increase in distension pressures did, however, occur in the absence of increased contractility. In fact, for viscous boluses there was a reduction in oesophageal contractility between studies 1 and 2 in the older group, in keeping with a loss of myenteric excitatory neurons (Meciano Filho et al. 1995, Johnson et al. 1998, Cowen et al. 2000, Phillips et al. 2003, Wade & Cohen 2004, Cammileri et al. 2008, Salles 2009). It is, therefore, likely that increased distension pressures during liquid swallows can be explained by reduced oesophageal distensibility in older persons (Gregerson et al. 2008), as pressure would increase if the same volume were accommodated in a smaller space. For liquid swallows this would serve to overcome distal OGJ flow resistance increasing the pressure differential across the OGJ.

The impedance ratio, a measure of oesophageal bolus retention increased in the older group compared to the younger and their own baseline, for viscous swallows. This finding is congruent with the observation in Chapter 6 of markedly increased viscous residue. Contractility reduced rather than increased and distension pressures also did not increase during viscous swallows so that the increased distal flow resistance (OGJ) cannot be overcome for increased consistencies. It is possible that in addition to centrally initiated primary peristalsis, a degree of peripheral “augmentation” induced by bolus-based distension

may occur in order to facilitate bolus transport for increased consistencies. Figure 8.4 shows an almost “linear” increase in oesophageal bolus residue across the time intervals and between younger and older persons, which is most significant in the oldest group in keeping with Soergel’s and Zobralske’s description of barium retention in the older old in the context of presbyesophagus (Soergel et al.1964, Zobralske et al. 1964).

8.4.3 Study Limitations

It has to be acknowledged that this study has limitations. While many more participants were studied, repeat studies with an interval of more than 12 months could only be achieved in a relatively small number of individuals. Despite this limitation, some differences demonstrated between groups remained significant and having individuals serve as their own baseline strengthened the statistical analyses within groups. This also mitigates the concern that some individuals, despite not reporting symptoms, could have subconscious awareness of abnormal swallowing which may prompt them to repeatedly volunteer for studies. While attempts were made to exclude intercurrent illness, many older individuals were on multiple medications, some which could have anticholinergic side-effects which may potentially affect oesophageal motility. Individuals were excluded when on medications with known major motility effects, including opioid medications. More males than females were included in the older group which may influence pharyngeal results due to differences in the size of the pharyngeal space.

8.4.4 Study Conclusion

To my knowledge, this is the first study using HRM-I to repeatedly study, at a time interval exceeding a year, multiple asymptomatic individuals across the age spectrum, including older old. In the pharyngo-UOS, changes were observed in keeping with UOS restriction, but in contrast with studies comparing different and slightly younger age cohorts (Shaker et al. 1993, Kern et al. 1999, Nativ-Zeltzer et al. 2016), hypopharyngeal contractility (peak pressure)

reduced over time in the older group. Furthermore, flow restriction was also observed at the LOS, along with a reducing oesophageal contractile response for increased consistencies in the older group. Oesophageal bolus retention increased significantly for increased consistency bolus in the older group, in the time interval between studies.

The finding of this study indicate that older old (over 85 years) persons may benefit from interventions to improve pharyngo-UOS swallowing by targeting pharyngeal strengthening and improved UOS opening. For oesophageal swallowing, increased consistency boluses may present a challenge for even the healthy older oesophagus. Careful consideration needs to be given to balancing swallowing safety and efficiency with quality of life.

Part III

Part III: Symptomatic Older Patients

Chapter 9 Pharyngeal High-Resolution Manometry with Impedance (P-HRM-I) in Older Patients

This Chapter includes data from older patients published as Omari et al. 2022 (Appendix A).

9.1 Introduction

Deglutitive disorders, representative of oropharyngeal dysphagia (OPD), are more common in older individuals (Cook 2009). This is due to an increased prevalence of vascular and neurodegenerative conditions occurring on a background of pre-existing swallowing function impairment (Cook 2009, Clavé and Shaker 2015, Rommel and Hamdy 2016).

Pharyngeal and upper oesophageal sphincter (Pharyngo-UOS) function had been comprehensively explored in asymptomatic healthy volunteers using pharyngeal high-resolution manometry with impedance (P-HRM-I) (Chapters 5 and 8). These exploratory works revealed that older patients had reduced UOS relaxation, a reduced extent of UOS opening distention, and an increased aspiration risk (swallow risk index - SRI), when compared to young persons. There was also an increase in the degree of UOS dysfunction, in older persons over a 4–6-year time interval from 80 years of age onwards, characterised in main by a further reduction in UOS opening distension and UOS flow resistance.

P-HRM-I is increasing in use for diagnosing and managing OPD (Doeltgen et al. 2017, O'Rourke et al. 2017, Cock & Omari 2017, Omari et al. 2020, Regan 2020, Jones & Colleti 2021, Heslin and Regan 2022, Bayona et al. 2022, Omari et al. 2022). An International working group recommended the use of several swallowing function variables (metrics), recorded during P-HRM-I (Omari et al. 2020) with the purpose of measuring pharyngeal muscle dysfunction, through the use of contractile integrals, and through the use of upper oesophageal sphincter (UOS) metrics measuring UOS relaxation (UOS-IRP), opening time, hypopharyngeal intrabolus pressures and the extent of opening distension/cross sectional area, through the use of maximum admittance (Cock et al. 2015), which requires impedance. In short, the goals are to determine contractile and sphincter function and, where available,

relate findings to swallowing radiology (termed video fluoroscopic swallowing studies or a modified barium swallow study).

Recently hypopharyngeal pressurization patterns had also been described and postulated to relate to UOS-restriction. (Omari et al. 2021). If these pressurization patterns relate to UOS-restriction, they would occur in older patients but also potentially in older controls. Hypopharyngeal pressurization patterns had not been previously assessed in an older cohort. Due to the observed abnormalities in UOS function in asymptomatic healthy older persons (termed UOS dysfunction, identified by an increased UOS-IRP with/without additional abnormal metrics), it is of interest to compare P-HRM-I in older patients with controls, including age-matched controls.

The aims of this study were: 1. determine which P-HRM-I derived variables distinguishes older patients from younger and age-matched controls, 2. Assess novel pharyngeal pressurization patterns in older patients, and where available, 3. assess radiology for evidence of swallowing dysfunction in terms of pulmonary aspiration and significant pharyngeal residue.

The hypothesis is that older patients would display additional abnormalities on P-HRM-I to those observed in asymptomatic older persons (described in Chapters 5 and 8).

9.2 Methods

9.2.1 Study population

Controls were selected from existing studies of asymptomatic healthy volunteers, studied using the same boluses and equipment as patients. Older participants were defined as those individuals 80 years of age and over. Patients were selected from a database of broad dysphagia studies undertaken in individuals who on clinical grounds were thought likely to have oropharyngeal dysphagia, based on typical symptoms including coughing or choking,

multiple swallowing, nasal regurgitation, or dysphagia in conditions known to be typically associated with oropharyngeal dysphagia such as stroke, motor neurone disease, Parkinson's disease, skeletal myopathies, and/or confirmed on radiology to have significant pharyngeal residue or aspiration etc. Patients were also grouped by age and those 80 years of age and older were defined as older patients for this study. Studies were included from the following ethics approvals: Southern Adelaide Human Research Ethics 403/10, 283/11, 215/13, 444/14, 552/13, 76/17, 188/17, 189/17. *Additional patient data were also added from ethically approved patient studies undertaken in Leuven, Sydney and Hong Kong: St Vincent's HospitalHuman Research Ethics Committee; Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research EthicsCommittee, NTEC 2019.183; Medical Ethics Committee Leuven approve number S58093 (17.7.2015)*

9.2.2 Manometry studies

Manometry studies (P-HRM-I) were undertaken according to methodology described in detail in Chapter 4. A typical study consisted of testing a minimum triplicate 5-, 10-, and 20-ml liquid (normal saline 0.9%) and viscous (Standardized Bolus Medium - SBM, Trisco Foods, Brisbane, Australia). Bread boluses (2x2cm, saline soaked were also frequently added). The consistencies used as per the International Dysphagia Diet Standardization Initiative (IDDSI) were 0 ,4 and 7. Not all individuals tolerated all consistencies. 5ml Liquid boluses in triplicate were tolerated by most individuals and for this reason, were used to report data. Data were exported for analyses via swallowgateway.com

9.2.3 Data analyses

Data analyses are described in more detail in Chapter 4.

Additional analyses of pharyngeal pressure patterns were undertaken where intrabolus pressurization waves were recognizable on P-HRM-I recordings considered suggestive of obstructed pharyngeal outflow resulting from impaired luminal distensibility or miss-timed

luminal opening; analogous to pressurizations reported in relation to ‘type 2’ esophageal achalasia and esophago-gastric junction outflow obstruction (Bredenoord et al. 2021, Omari et al. 2021).

Swallows were qualitatively assessed for presence of intrabolus pressurization patterns exceeding 20mmHg with the pressure heat-map colour scale set to range -10mmHg (blue) to 100mmHg (red). Three different pressurization patterns were characterized (Omari et al 2021). Sustained pressurizations occurring for the majority of UOS relaxation period were subtyped into those with no visible stripping contraction and a simultaneous pan-pressurization (Type 1) and those terminated by arrival of an intact stripping contraction (Type 2). Transient pressurization patterns (Type 3) occurred for brief periods during the early-mid phase of UOS relaxation and terminated before arrival of the stripping contraction – Type 3 patterns are also seen in small proportion of controls (Figure 9.1).

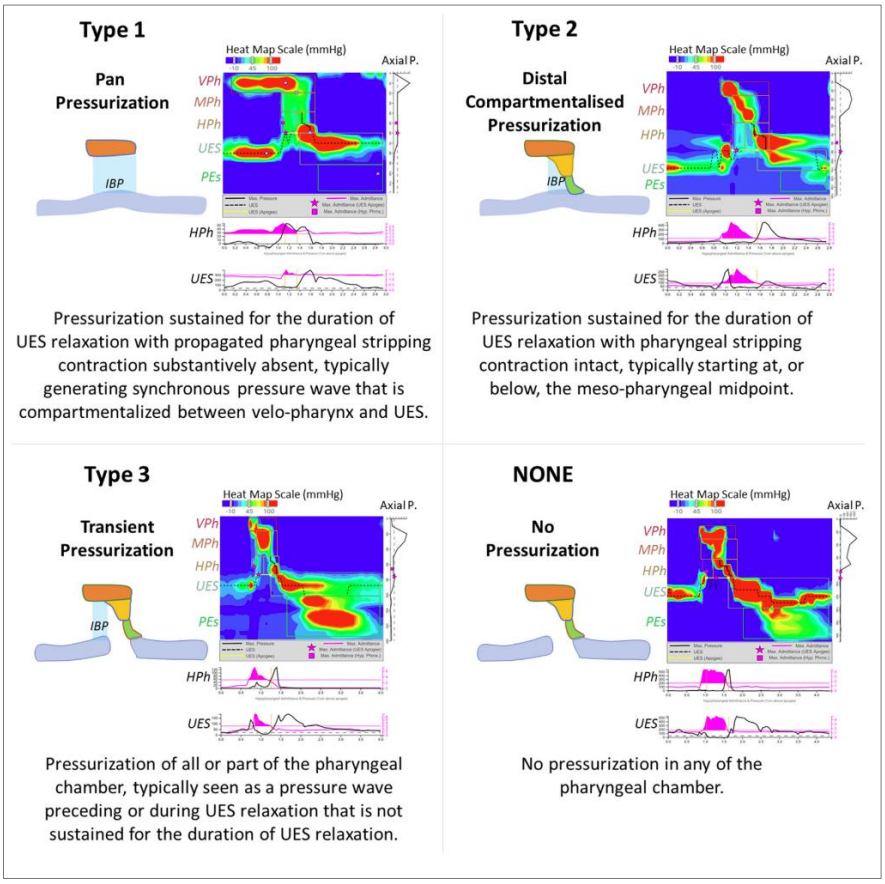


Figure 9.1 Hypopharyngeal pressurization patterns (see text for detail).

9.2.4 Statistical analysis

Statistical analyses were undertaken using Sigmaplot 14.0 (Systat software, San Jose, Ca) and GraphPad Prism v 9.4 (GraphPad Software, San Diego, Ca). One-way ANOVA or Kruskal Wallis test was conducted across group, with significant results followed up by post-hoc Holm-Sidak or Dunn with Bonferroni correction. Proportions were analysed using Chi-square analyses. A P-value of <0.05 was considered significant.

9.3 Results

9.3.1 Study population

Table 9.1 Study population

	Younger		Older	
	Controls	**Patients**	**Controls**	**Patients**
Number (n=)	101	454	20	47
Age (Years ±St Dev)	51±18	62±12	85±4	84±3
Sydney Swallow Questionnaire	34±5	365±36	73±11	514±147

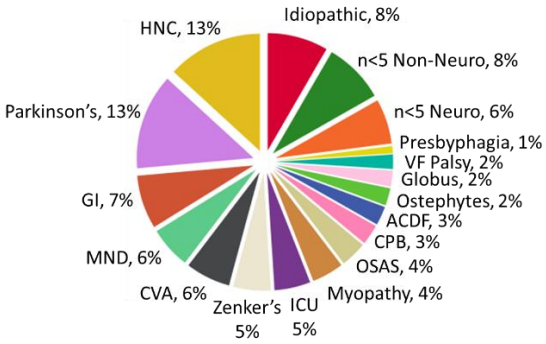


Figure 9.2 Diagnostic Groups
Subgroups represented by ≥5 individuals are delineated, the remainder are classified as idiopathic, non-neurological or neurological. *Abbreviations:* VF, Vocal Fold; ACDF, Anterior Cervical Discectomy and Fusion surgery; CPB, Cricopharyngeal Bar; OSAS, Obstructive Sleep Apnea Syndrome; ICU, Intensive Care Unit Admission; Zenker's, Zenker Diverticulum; CVA, Cerebrovascular Accident (Stroke); MND, Motor Neuron Disease; GI, Gastrointestinal Disease; Parkinson's, Parkinson Disease; HNC, Head and Neck Cancer

9.3.2 Pharyngeal and UOS Metrics

Table 9.2 Pharyngeal and upper oesophageal sphincter metrics per group

	Younger		Older	
	Controls	**Patients**	**Controls**	**Patients**
Pharyngeal Contractility				
PhCI (mmHg.s.cm)	272±14	267±7	311±40	268±30
VCI (mmHg.s.cm)	85±8	96±4	100±18	90±13
MCI (mmHg.s.cm)	101±6	96±3	138±20	107±12
HCI (mmHg.s.cm)	72±5	74±3	74±9	72±8
UOS Metrics				
IBP (mmHg)	5.5±0.7	**10.9±0.6$^{\$\$}$**	**18.2±4.7**	**10.1±1.5**
UOS IRP (mmHg)	-2.2±0.5	**6.7±1.3$^{\$\$\$}$**	**6.2±2.1**	**5.5±1.6**

UOS RT (sec)	0.571±0.010	0.559±0.006	0.585±0.024	0.571±0.021
UOS Max Ad (mS)	6.6±0.2	**4.6±1.3$^{\$\$}$**	5.9±0.4	**4.3±0.2$^{\$\$}$**
Global Metric				
Swallow Risk Index	2[1;3]	**4[2;11]**	**6[2;10]**	**5[2;9]**
Radiology				
PAS (Rosenbek)	1[1;2]	**2[1;7]**	2[1;2]	**3[1;8]**
NRRSv	0.05±0.03	**0.55±0.07$^{\$\$\$}$**	0.09±0.05	**0.41±0.11$^{\$}$**
NRRSp	0.04±0.04	**0.37±0.08$^{\$\$}$**	0.15±0.10	**0.42±0.11**
Additional Pressure-Flow Metrics				
BPT (sec)	0.684±0.019	**0.952±0.035$^{\$\$}$**	**1.018±0.108**	**0.862±0.091**
DCL (sec)	0.524±0.009	**0.441±0.005$^{\$\$}$**	0.532±0.028	**0.439±0.022$^{\$}$**
PeakP (mmHg)	154±8	**123±4$^{\$\$\$}$**	176±20	**127±15$^{\$}$**
UOS-BP (mmHg)	74±4	**60±2$^{\$}$**	65±12	**38±6$^{\$}$**

Bold text: P < 0.05 vs. Controls; $^{\$}$ P < 0.05, $^{\$\$}$ P < 0.01, $^{\$\$\$}$ P < 0.001 vs. Age-matched Controls;
Median five swallows per individual patient.

There were no differences between older patients and younger or age-matched controls for any of the pharyngeal contractile variables.

UOS-IRP was increased in older patients (P < 0.001) and also in older controls (P < 0.001) compared to younger controls (Table 9.2, Figure 9.3). Other UOS metrics which also identified patient groups were hypopharyngeal intrabolus pressure (IBP) and UOS Max Ad (Table 9.2, Figure 9.3). In older patients, US Max Ad was reduced compared to older controls (P < 0.01, Table 9.2)

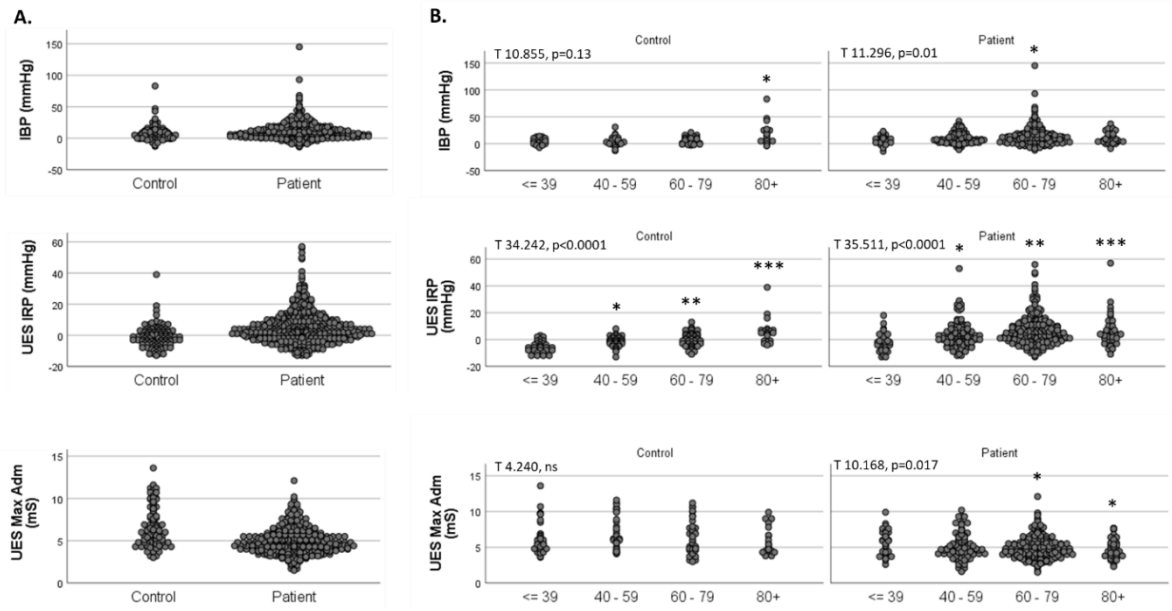


Figure 9.3. Data distribution for key UOS variables.
A. Group (see Table 1 for significance). **B.** Age sub-groups differences within Controls and Patients. Compared by Independent Samples Kruskal-Wallis Test (T, p-value) *indicates pairwise difference to <=39 years comparisons adjusted by Bonferroni correction for multiple tests (*p<0.05, **p<0.005, ***p<0.0001).

The global metric, swallow risk index was increased in older patients and also in older controls, compared to controls (P < 0.5, Table 9.2).

Additional pressure-flow metrics not currently part of the Intranational working party criteria, namely bolus presence time (BPT), distention contraction latency (DCL), hypopharyngeal peak pressure (PeakP) and upper oesophageal sphincter baseline pressure (UOS-BP) all distinguished older patients from younger controls (P < 0.05, Table 9.2). DCL, PeakP and UOS-BP was also reduced in older patients compared to age-matched controls (P < 0.05, Table 9.2).

Pharyngeal Pressurization Patterns

Table 9.3 Hypopharyngeal pressurization patterns (by group).

	Younger		Older	
	Controls	**Patients**	**Controls**	**Patients**
None	86	252	11	25
Type 1	0	28	0	5
Type 2	0	51	3	2
Type 3	15	121	6	9

Older patients had more abnormal pharyngeal pressurization patterns compared to younger controls (Chi-square, P < 0.001) but not compared to older controls.

9.3.3 Radiology

Radiology was frequently undertaken using non-standardized boluses and such radiology studies were not included in the analyses. Despite this limitation, aspiration and vallecular (NRRSv) and pyriform (NRRSp) residue were increased, using the most objective criteria available (See Chapter 4), in all older patients compared to controls (P < 0.05, Table 9.2). Within the older group only vallecular residue was significantly increased when comparing older patients to age-matched controls (P < 0.05, Table 9.2).

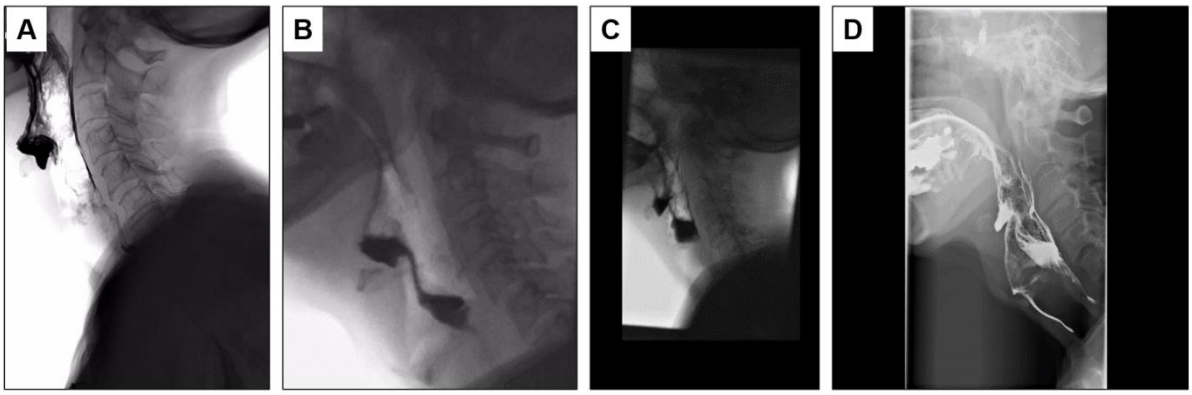


Figure 9.4 Examples of radiology in older patients: A.83F Parkinson's disease: vallecular residue B. 81M Brain stem stroke: vallecular and pyriform residue. C. 80F Myopathy: vallecular and pyriform residue D. 90M Motor Neuron disease with evidence of vallecular, pyriform residue and airway spillage.

9.4 Discussion

This study focused on the findings in older OPD patients, investigated using P-HRM-I, comparing metrics with both younger and age-matched controls. As some abnormalities, for example an increase in UOS-IRP had been observed in asymptomatic healthy older persons (Chapters 5 and 8, Nativ-Zeltzer 2016), it was of particular interest to identify *additional* abnormalities that would distinguish older patients from matched controls.

Hypopharyngeal pressurization patterns did not differ between older patients and age-matched controls. In addition to UOS-IRP and hypopharyngeal intrabolus pressures, which were equivalently increased in older patients and controls (compared to younger controls), UOS maximum admittance, a correlate of UOS cross-sectional area, was significantly reduced in older patients, compared to both younger and age-matched controls ($P < 0.01$). Of the currently accepted P-HRM-I metrics (Omari et al. 2020), UOS MaxAd was the *only* metric which distinguished older patients from age-matched controls. The implication of this finding is that older patients have abnormalities superimposed on reduced UOS opening and in older patients there is a greater degree of UOS narrowing, making addressing UOS opening an attractive target for interventions regardless of the underlying cause.

Several additional metrics, not part of the current subset of accepted metrics, were assessed for their ability to distinguish older patients from age-matched controls. Hypopharyngeal bolus presence time (BPT) was increased in older patients, but equally so in older controls. In the context of UOS restriction it is unsurprising that the bolus dwells in the hypopharynx for a pronged period. Three additional P-HRM-I metrics did, however, distinguish older patients from age-matched controls: hypopharyngeal peak pressure (peakP), distension contraction latency (DCL), and the upper oesophageal sphincter basal pressure (UOS-BP). Out of interest, these three metrics also distinguished younger patients from younger controls.

Hypopharyngeal peak pressure may be an important and clinically relevant measurement P-HRM-I. As a maximal pressure, it represents the lumen occlusive force applied by the bolus tail sweeping down the pharynx clearing pharyngeal contents. As contractile integrals are confounded by including increased duration increased measurements may not be as clinically relevant (as peak pressures alone).

We observed in this study that a shorter duration DCL distinguished patients from age-matched controls. The distention to contraction latency (DCL) is a somewhat complex metric to understand. Changes in distension-contraction timing may indicate altered lingual bolus propulsion as well as in the neural sensory feedback loop to nucleus tractus solitarius altering pharyngeal motor neurone outputs in an attempt to alter the functional swallow outcomes. In an obstructed pharynx shorter DCL has been associated with failure of transit with retrograde escape behind the pharyngeal stripping wave.

Radiology was assessed, as it is regarded by many as the gold-standard assessment for OPD. Abnormal radiology distinguished all patients (younger + older) from younger controls. However, only increased vallecular residue, measured using the NRRSv (Pearson et al. 2013), distinguished older patients from age-matched controls. These findings are suggestive that P-

HRM-I may be more sensitive than radiology in distinguishing older patients from those with only ageing related changes. More complete comparative data in older cohort will be needed.

The study has some limitations. Only a single bolus volume and consistency was assessed. We know some metrics, especially the more sensitive metrics of UOS restriction, such as UOS Max Ad may change significantly with changes in bolus volume or consistency (Ferris et al. 2021). It is quite likely that such changes will exacerbate any pre-existing abnormalities and, larger bolus volumes for example, may better distinguish UOS flow restriction when measuring IBP (Williams et al. 2002, Pal et al. 2003). Regardless, while 5ml bolus volume could be swallowed by all participants, this was not the case for larger volumes. The limitation as regards radiology had been briefly discussed above and argues for the use of standardised protocols during radiological studies.

In conclusion, few metrics distinguished older patients from older controls. Of currently accepted P-HRM-I metrics only UOS Max Ad distinguish older patients from age-matched controls. Several additional P-HRM-I metrics showed promise for distinguishing older patients, including two pressure-based metrics: mean hypopharyngeal peak pressure and the upper oesophageal sphincter basal pressure. Distension contraction latency also distinguished older patients form age-matched controls. Further exploration of the clinical utility of added metrics would be of value not only in older but in all OPD patients.

Chapter 10 Increased prevalence of major oesophageal motor disorders and impaired bolus clearance in symptomatic older patients

Abstract

Background and Aim: Current data on oesophageal motility disorders in ageing are conflicting with some historical studies showing increased major motility disorders in older patients, while others observed no differences when compared to younger patients. We aimed to compare the outcomes of motility studies across age cohorts.

Methods: We selected studies performed for dysphagia, chest pain or typical reflux symptoms for patients aged over 20 years of age for the years 2015 to 2019. Incomplete, post-surgical, or studies done for other indications, were excluded. Patients were studied in right lateral posture using MMS Solar high-resolution impedance manometry: 32/36 pressure at 1cm, 16 impedance 2cm length (MMS/Unisensor, Laborie, Enschede, Netherlands). Liquid (10x normal saline 0.9%), viscous and solid boluses were administered. Data were reported according to the prevalent Chicago Classification (V3.0). Proportional data were compared via Chi-square tests (GraphPad Software, San Diego, Ca, US). A P-value < 0.05 was considered statistically significant.

Results: Data from n=1185 studies were included in groups as following 20-39 yrs: n = 175; 40-59 yrs: n= 420; 60-79 yrs: n= 499; 80 plus yrs: n=91. Major disorders of distal oesophageal motility were increased in patients aged 60-79 yrs of age (P = 0.03 vs. 40-59 yrs; P = 0.005 vs. 20-39 yrs) and in those 80 plus yrs of age (P < 0.001 vs. all other ages). For each symptom one diagnosis occurred more frequently in over 80 yrs, compared to other ages – dysphagia: distal oesophageal spasm (P = 0.002); chest pain: absent contractility (P = 0.001) and typical reflux symptoms: achalasia (P < 0.001).

Conclusion: Major disorders of distal oesophageal motility occurred more commonly with increasing age. Relatively fewer patients in the oldest cohort were referred for investigation of symptoms when these data suggest older symptomatic patients should perhaps be referred more often to identify treatable major motility disorders.

10.1 Introduction

Whether oesophageal diagnosis of motility disorders occur more frequently in older patients remains unclear. While studies have shown increases in diagnoses of achalasia or spastic motility in older patients (Ribeiro et al. 1998, Andrews et al. 2009), others have shown no differences (Robson & Glick 2003, Andrews et al. 2008, Nakato et al. 2017, Shim et al. 2017). Few studies exist using high-resolution manometry and the Chicago classification and none assess oesophageal bolus transit.

Motility investigations in older patients have employed different definitions of ageing. Studies have used ages ≥ 50 years (Jung et al. 2015, Dantas et al. 2010), 60 years (Richter et al. 1987, Khan et al. 1977), 65 years (Grande et al. 1999, Robson & Glick 2003, Kawami et al. 2015, Shim et al. 2017, Nakato et al. 2017, Andrews et al. 2009), 70 years (Ferrioli et al.1998, Nishimura et al. 1996), 75 years (Ribeiro et al. 1998) and 80 years of age (Andrews et al. 2008, Besanko et al. 2011, Besanko et al. 2014) to define older age. Inconsistent findings are therefore not surprising. The age around which aging-related oesophageal dysfunction (called “presbyesophagus”) occurs is unclear. Such changes have variously been described as occurring in patients in their nineties (Soergel et al. 1964) or eighties (Cock et al. 2016, Weerakkody & Sharma 2021). Some authorities have considered this to be due to intercurrent illnesses, rather than ageing (Tack & VanTrappen 1997, DeVault 2002). Our understanding of aging affects is also influenced by evolution of technology and a classification system for diagnosing oesophageal dysmotility.

Reports of lower oesophageal sphincter resting pressure and relaxation vary. Some studies show an increase in the proportion of older symptomatic patients with an increased IRP4, implying reduced LES relaxation (Besanko et al. 2011, Djiinbachian et al. 2021). However, similar observations of reduced LES relaxation have been described in older asymptomatic healthy volunteers (Khan et al. 1977, Besanko et al. 2014, Jung et al. 2015, Cock et al. 2017).

Other studies, using lower age thresholds, have not shown these differences in LES relaxation (Richter et al. 1987, Nishimura et al. 1996, Ferriolli et al. 1998, Nakato et al. 2017, Shim et al. 2017). As the Chicago classification algorithm starts by considering LOS relaxation (abnormal IRP4), reduced relaxation in older persons may significantly increase the likelihood of an abnormal diagnosis. To date, this has not been clinically observed or recognised in routine clinical practice.

In terms of contractility, some past studies have observed reduced amplitude and increased failure of peristaltic contractility in older persons (Khan et al. 1977, Grande et al. 1999, Nishimura et al. 1996, Andrews et al. 2008, Cock et al. 2016). Again, this had been observed both in healthy volunteers (Cock et al. 2016) and in some patient cohorts (Khan et al. 1977, Grande et al. 1999, Nishimura et al. 1996, Andrews et al. 2008). There has been very little assessment of how such reduced contractility may impact on oesophageal function in terms of clearance (Cock et al. 2016) and there are currently to our knowledge no studies reporting impedance measured oesophageal bolus transit in older patients. Reduced and incoordinate contractility had been described as part of the primarily radiological description of presbyesophagus, where it was linked to incomplete oesophageal bolus clearance (Zboralske et al. 1964).

In summary, some existing data show reduced LES relaxation and weaker oesophageal contractility in older persons, including healthy volunteers over eighty years of age. To date, most studies, especially those with lower age cut-offs, have not described any marked influence of age on manometric diagnoses; including studies using high-resolution manometry and the Chicago classification (Shim et al. 2017, Nakato et al. 2017, Djiinbachian et al. 2021). Indeed, one study by Nakato et al. (Nakato 2017), demonstrated a greater proportion of major motility disorders in *younger* patients with dysphagia (39% vs 28%).

We therefore conducted an audit of our existing manometry database of patients studied via high-resolution manometry for gastrointestinal symptoms (dysphagia, chest pain or typical reflux symptoms) in the Southern Adelaide region. Our study had the following aims:

1. To compare the frequency of diagnosis of oesophageal motility disorders using high-resolution impedance manometry and the Chicago classification in different age cohorts; and
2. to assess the associated changes in oesophageal bolus clearance.

10.2 Methods

10.2.1 Population

A clinical manometry database of investigations performed between January 2015 and December 2019 was searched and this identified 1260 cases referred for primary dysphagia, chest pain and/or typical reflux symptoms. Informed consent for audit purposes had been obtained at the time of investigation (Protocol HREC/13/SAC/215.13 Southern Adelaide Clinical Human Research Committee). Seventy-five were then excluded (28 incomplete; 40 post-upper GI surgery; 7 <20 years old) leaving 1185 studies which were grouped by age (20-39, 40-59, 60-79 and ≥ 80 years).

10.2.2 Manometry studies

Per clinical routine, patients withheld all medications (if possible) known affect distal oesophageal motility (e.g., prokinetics, serotonin receptor inhibitors, opioids, some anti-depressants). Patients completed symptom questionnaires including BEDQ (Taft et al. 2016), GERD-Q (Jonasson et al. 2013). Manometry catheters (Unisensor) were prepared via manufacturer instructions, including pre-soaking catheters in body temperature water to minimize pressure sensor drift. The manometry assembly consisted of either a 2.7mm or 3.2mm diameter impedance manometry catheter. These catheters had between 32 and 36 one-centimetre spaced pressure sensors, and sixteen, two-centimetre length impedance segments. Recordings aquired at 20Hz using an MMS Solar system with Unisensor catheters

(MMS/Laborie, Enschede, Netherlands; Unisensor catheter, Unisensor/Laborie, Attikon, Switzerland).

After an overnight fast, patients were intubated via an anaesthetized nostril (2% lignocaine gel). The standardized swallow challenge protocol consisted of 10x5ml liquid (normal saline) boluses in a right lateral or supine posture followed by 5x2ml "multiple rapid swallowing" manoeuvres (MRS). Following MRS, the patients were asked to sit upright with head in neutral position to swallow five 5ml standardized viscous and five 2x2cm solid (saline-soaked bread) boluses. Swallow-by-swallow symptoms (bolus perception) were assessed, using a 10 cm visual analogue scale; 0cm indicating no perception and 10cm the bolus being stuck and chest pain.

Following completion of the study procedure, patients were given refreshments and observed for one hour, before leaving the unit.

10.2.3 Bolus Clearance

Complete bolus transit was defined as a drop in impedance measurement to 50% of baseline, with a subsequent return above 50% for individual impedance sensors through the body of the oesophagus and lower oesophageal sphincter (LOS) (Sifrim et al. 2004) with failure of a drop and return in no more than a single channel.

For complete liquid bolus clearance, complete bolus transit was required for 80% of swallows. For clearance of increased consistencies, complete bolus transit was required for 70% of swallows (Tutuian et al. 2003).

10.2.4 Data Analyses

Manometry studies were reported by one of four clinicians (CC, RF, RH, JH; all with more than five years' experience reporting motility studies) using MMS diagnostic and reporting software

version 9.5F (and prior to 2016, version 2.3). As part of clinical routine, a second opinion was sought for achalasia diagnosis.

Demographic data was reported by age group. Data from the 5ml liquid challenges was used per convention at the time to report the Chicago Classification (version 3.0) of distal oesophageal motility (Kahrilas et al. 2015). System-specific normative values were applied. Ineffective oesophageal motility (IEM) and fragmented contractility were treated collectively as “minor disorders” of peristalsis. We used 20mmHg as the normative cut-off for IRP_4 and all other values are the same as that reported by Chicago (Kahrilas et al. 2015; Yadlapati et al. 2021). Data on provocative manoeuvres were analysed post-hoc and are reported on separately (Chapter 11).

10.2.5 Statistical analysis

Proportions were compared using Chi-square tests using Graphpad Prism v 8.4 (GraphPad Software, San Diego, Ca, US). A P-value of < 0.05 was regarded as statistically significant.

10.3 Results

10.3.1 Indications and Findings

Numbers and proportions of 1185 manometry procedures done for each of three indications (dysphagia, chest pain & reflux) in age cohorts are summarized in Table 1.

Table 10.1 Proportion of studies done for each indication by age

	Dysphagia	Chest Pain	Reflux	Total
20-39 yrs n(%)	41(9)	37(14)	97(22)	175(15)
40-59 yrs n(%)	153(34)	93(32)	174(39)	420(36)
60-79 yrs n(%)	199(44)	136(48)	164(36)	499(43)
80 ys plus n(%)	63(13)	16(6)	12(3)	91(8)
Total	**454**	**282**	**447**	**1185**

The findings in terms of motility disorders are summarized in Figure 1. Major disorders were increased in older patients: 60-79 years of age (P = 0.03 vs. 40-59 years; P = 0.005 vs. 20-39 years of age) and 80 years and over (P < 0.001 vs. all other age cohorts). Minor disorders occurred in a similar proportion between age groups, while normal studies were seen less frequently in the older patients (P < 0.001 vs. all other age cohorts).

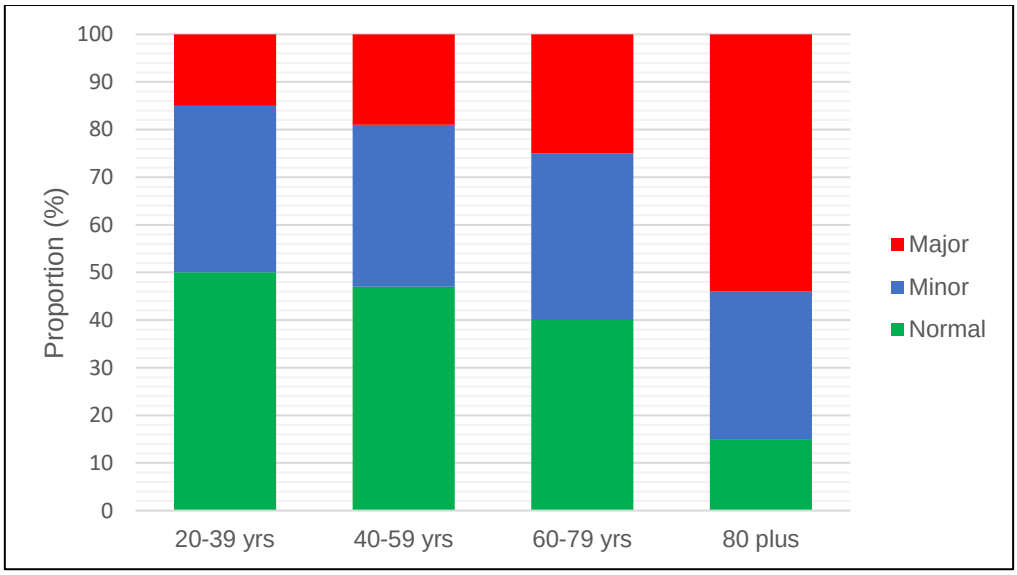


Figure 10.1. Oesophageal motility disorders by age.

The 60-79 yrs age group constituted the largest proportion of studies (43%) and equivalent proportion (44%) of major disorders. In contrast, despite only constituting approximately 8 percent of the entire cohort, the oldest cohort made up 18 percent of all major disorders diagnosed.

10.3.2 Findings per Baseline Symptom

Chicago classification findings for each baseline symptom (per age) are summarized in Figures 2-4 and Table 2 below:

DYSPHAGIA

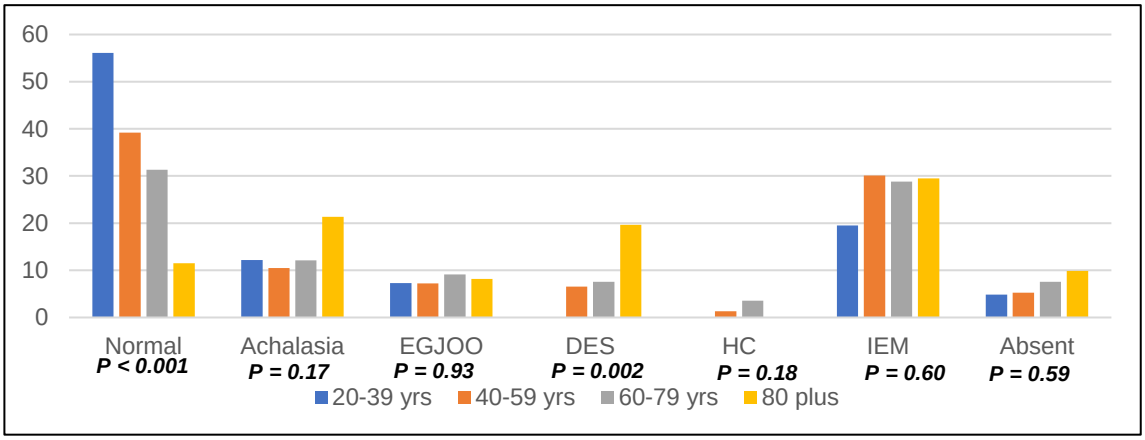


Figure 10.2. Diagnoses in patients with Dysphagia as primary presenting symptom (by age)

EGJOO – Oesophagogastric junction outflow obstruction; DES – Distal oesophageal spasm; HC – Hypercontractile; IEM – Ineffective oesophageal motility

CHEST PAIN

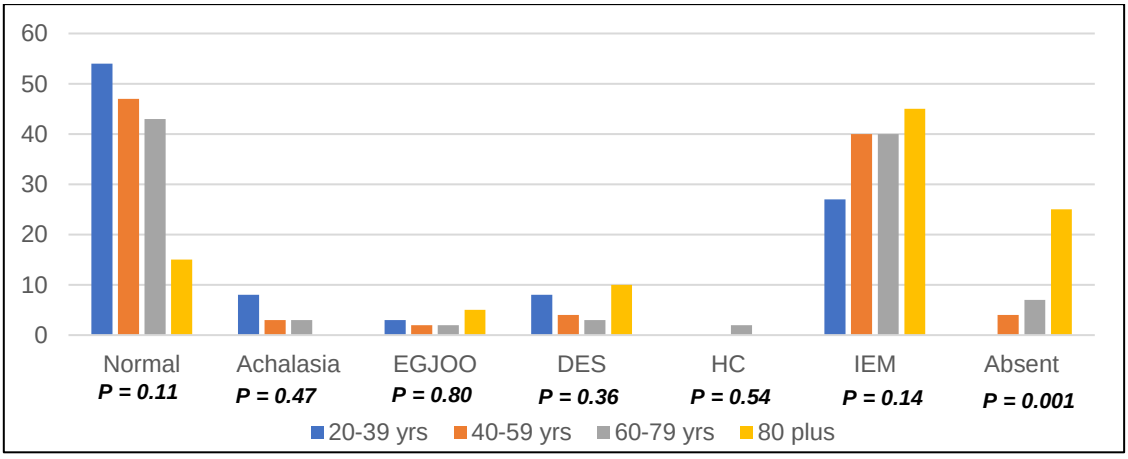


Figure 10.3. Diagnoses in patients with Chest Pain as primary presenting symptom (by age)

EGJOO – Oesophagogastric junction outflow obstruction; DES – Distal oesophageal spasm; HC – Hypercontractile; IEM – Ineffective oesophageal motility

REFLUX

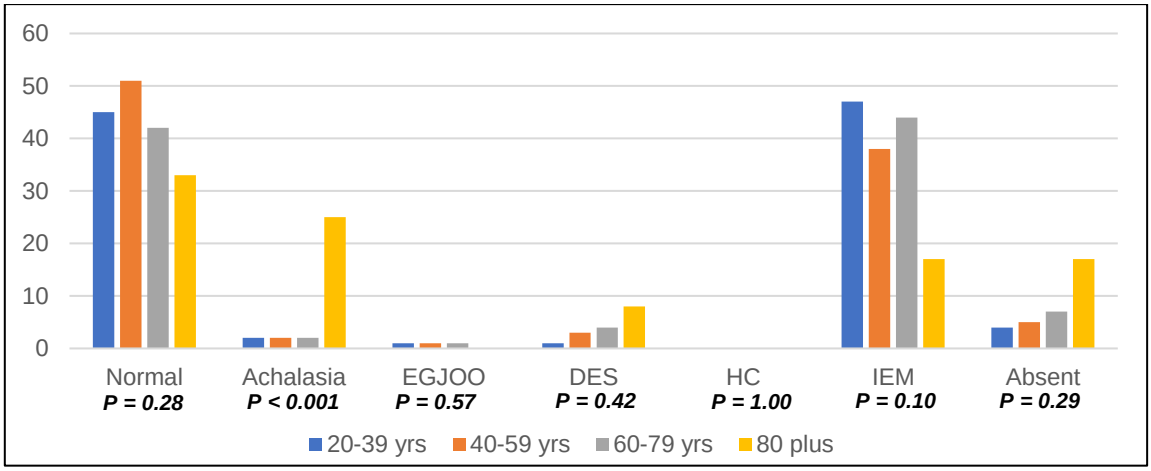


Figure 10.4. Diagnoses in patients with Reflux as primary presenting symptom (by age)

EGJOO – Oesophagogastric junction outflow obstruction; DES – Distal oesophageal spasm; HC – Hypercontractile; IEM – Ineffective oesophageal motility

Table 10.2 Number of patients with Chicago Classification diagnoses, per age.

	Normal	Achalasia	EGJOO	DES	HC	IEM	Absent
20-39 yrs	86	10	5	4	0	61	6
40-59 yrs	193	22	14	19	2	140	21
60-79 yrs	194	31	22	26	9	168	33
80 plus	14	16	6	15	0	28	12

EGJOO – Oesophagogastric junction outflow obstruction; DES – Distal oesophageal spasm; HC – Hypercontractile; IEM – Ineffective oesophageal motility

Most studies overall were either normal (31%) or minor disorders (25%). The proportion of minor disorders is in keeping with that previously reported in normal healthy volunteers (Cock 2016). Major disorders were rare, with the most common major disorders in this study being achalasia and oesophago-gastric junction outflow obstruction (EGJOO). These were more prevalent in the oldest group where they appeared to be associated with specific symptoms: dysphagia -distal oesophageal spasm ($P = 0.002$); chest pain - absent contractility ($P = 0.001$), and reflux symptoms - achalasia ($P < 0.001$).

10.3.3 Bolus Clearance

Complete liquid bolus clearance was slightly reduced in the oldest group (Table 3). It was notable that some older patients with *normal* distal oesophageal peristalsis had incomplete liquid clearance due to proximal bolus escape (Figure 10.5). Complete viscous and solid clearance was further reduced in the oldest age group (Table 3).

Overall, bolus clearance reduced with increasing age, consistency, and diagnostic category. Effective solid bolus clearance was not observed *at all* in the oldest (>80 years of age) cohort.

Table 10.3 Bolus clearance (%) for liquid, viscous and solid boluses, by age

	Liquids			*Viscous*			*Solids*		
Chicago:	**Normal**	**Minor**	**Major**	**Normal**	**Minor**	**Major**	**Normal**	**Minor**	**Major**
20-39 yrs	100	77	16	80	50	6	67	33	10
40-59 yrs	100	62	11	83	40	6	53	47	3
60-79 yrs	100	53	7	67	29	10	27	12	3
80 plus	80	33	0	20	18	0	0	0	0

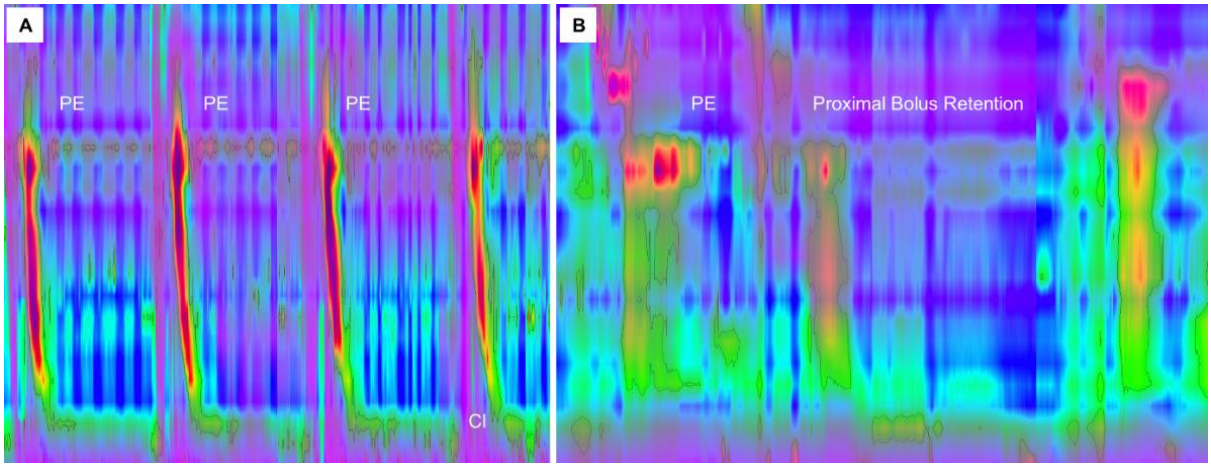


Figure 10.5. Proximal bolus escape in an older patient. A: Normal distal oesophageal motility in an eighty-year-old with proximal bolus escape (PE) of liquid swallows and eventual bolus clearance (Cl). B: During viscous swallows, aberrant swallow patterning, and more prominent proximal bolus escape (PE) and retention can be seen.

10.4 Discussion

We conducted an audit of manometric studies undertaken in our unit between 2015 and 2019 with the aim of comparing motility disorders between different age cohorts.

In this study comparing motility disorders amongst different patient age groups. Major disorders of distal oesophageal contractility occurred more often in patients over sixty years of age, when compared to younger cohorts. Furthermore in those over eighty years distal oesophageal spasm was increased in those with dysphagia, absent contractility in those with chest pain, and achalasia in those with typical reflux symptoms

The prevalence of complete bolus clearance reduced with age and increasing severity of Chicago classification diagnosis. The age-related impairment of bolus clearance became increasingly evident when heavier consistency boluses were swallowed. Indeed, we could not demonstrate normal solid bolus transit in any of the oldest cohort studied. These findings contrast with past studies which included a smaller sample size (Ribeiro 1998, Andrews 2008, Andrews 2009, Robson & Glick 2003, Besanko 2011, Nakato 2017, Shim 2017) or used lower age cut-offs (Andrews 2009, Shim 2017, Nakato 2017).

Dysphagia remained the most common reason for referral of older patients and spastic motor disorders were diagnosed more often in these older patients, as has been reported previously (Andrews et al. 2008, Ribeiro et al. 1998). In patients with chest pain, absent contractility, rather than spastic motility disorders was increased. The most likely explanation for chest pain in older patients with absent contractility is the increased presence of complicated reflux disease. (DeVault 2002, Collen et al. 1995, El-Serag et al. 1997, Zimmerman et al. 1997). Another potential explanation is that reduced or failed bolus clearance associated with absent contraction leads to perceived bolus entrapment (Cock et al. 2020).

The finding of an increased prevalence of achalasia in older patients (>80 years of age) with typical reflux symptoms has important clinical implications. In many cases symptoms in older patients are disregarded or regarded as a natural part of the ageing process. Older reflux patients are also less likely to be referred for motility studies which, in this context, are often conducted to plan anti-reflux surgery. Our study suggests older patients with reflux symptoms may be at risk of a missed diagnosis of achalasia or EGJOO, and referral should be considered for motility studies, especially when regurgitation occurs prominently. This is particularly important as many of these cases are potentially amenable to interventions. Peroral endoscopic myotomy (POEM) has proven to be feasible in older achalasia patients with high rates of success (Li et al. 2015). Even when dilatation, surgery or POEM is not possible in the setting of achalasia, older patients appear to do better than younger groups following botulinum toxin injection (Heddle & Cock 2020).

Bolus clearance was markedly reduced in older patients with a Chicago Classification disorder. This observation was even more marked for increased bolus consistencies. Past studies have shown a role for increased consistencies to add to the diagnosis of motility disorders and in the context this may apply even more so in older patients (Dalmazo et al 2012, Sweis et al. 2014, Ang et al. 2017, Fox et al. 2021). Our previous studies had shown

that reduced bolus clearance occurred even in older healthy volunteers, over eighty years of age (Cock et al. 2016). In this previous study, bolus clearance was only 40% for increased consistencies in asymptomatic older healthy volunteers. These findings were congruent with the 51-56% radiological solid bolus escape described by Jou et al. (Jou 2009) at the levels of the aortic arch and EGJ, respectively, in older (>65 yrs) healthy volunteers. Normative cut-offs for % bolus clearance (Tutuian et al. 2003, Sifrim et al. 2004) may have to be adjusted in older persons. However, even if we accept a reduced normative cut-off value for increased consistency bolus in older groups (60% liquids; 40% increased consistencies), failed clearance occurred commonly in patients. In the context where bolus retention may relate to bolus perception (Cock et al. 2020), we hypothesise that in older patients with dysphagia, bolus retention, including proximally (see figure 5) may cause symptoms such as dysphagia, possibly related to increased sensory perception to bolus-based distension in this anatomical region (Rao et al. 1996, Woodland et al. 2015), which in the older population has been shown to be less compliant (Gregerson et al. 2008).

The limitations of a retrospective review are acknowledged, including a risk of bias in referral patterns – e.g., older patients were potentially only referred once they had longstanding and major symptoms while younger patients may have been referred earlier in many cases. Disorders of reduced EGJ relaxation were common in older patients but also occurred in a previous study of controls over eighty years of age (Cock 2017), which challenges the results for disorders of impaired EGJ relaxation in older patients. We propose a definitive diagnosis in this setting needs added evidence from radiology or Endoflip measurement of EGJ distensibility (Rohof et al. 2012, Triggs et al. 2019). While additional assessment of upright liquid intrabolus pressures had been proposed (Triggs et al. 2019, Yadlapati et al. 2021, Kahrilas et al. 2021) as an adjunct measure in EGJOO, it is unlikely this measure will be meaningful in the context of weak or failed peristalses, which occurred commonly in the older cohort. It is not currently known whether any alternative impedance-based metrics (Carlson et al. 2017) may be useful in further assessment of oesophageal or EGJ function in this context.

In conclusion, this study showed increased major disorders of distal oesophageal motility and reduced bolus clearance in aging. Specific diagnoses were increased by primary symptom and of most clinical relevance a diagnosis of achalasia was increased in older patients presenting with typical reflux symptoms. Clinicians should be encouraged to send more older individuals for manometry in order to identify potentially treatable causes of distal oesophageal motility.

Chapter 11 Oesophageal pressure-flow analysis, provocative swallowing, and correlations of age with oesophageal metrics.

11.1 Introduction

Past motility studies in older patient groups have produced inconsistent results (Ribeiro et al. 1998, Grande et al. 1999, Robson & Glick 2003, Kawami et al. 2015, Shim et al. 2017, Nakato et al. 2017, Andrews et al. 2009), however the analysis undertaken as part of this research program showed a very clear increase in the proportion of diagnoses of major distal oesophageal motility disorders, as reported through the Chicago classification, in older patients over 80 years of age (Chapter 10).

Oesophageal and OGJ changes had also been observed in older healthy volunteers (Chapters 7 and 8). These changes can be summarised as being consistent with reduced contractility, lower oesophageal sphincter (LOS) relaxation and oesophageal bolus clearance. This combination of abnormalities produces an achalasia-like pattern, and it is possible that some older patients diagnosed as having achalasia or oesophago-gastric junction outflow obstruction may in fact overlap with normal older persons. It is thus of interest to determine if there are differences in older patients (≥80 years of age), as compared to younger patients (aged 18-79 years of age) but also with age-matched control groups.

Some changes have been described in oesophageal physiology in older patients in keeping with the historical descriptions of presbyphagia. Studies using high-resolution manometry have correlated Chicago classification metrics with age and found IRP4 to be correlated (Jung et al 2015, Djiinbachian et al. 2021). No studies in older patients have assessed multiple rapid swallowing, impedance-based metrics, or oesophageal bolus clearance, comparing to younger.

Aims of this study were to 1. compare symptomatic older patients (80 years of age and older) with younger patients, and age-matched controls; 2. assess multiple rapid manoeuvres in older patients with weak contractility; and 3. correlate age with high-resolution manometry impedance metrics.

11.2 Methods

11.2.1 Study Population

The study population was a sub-population of the population described in Chapter 10 who had undergone additional pressure-flow analysis and/or provocative swallowing manoeuvres. Controls were selected from previously studied control subjects. The non-obstructive dysphagia population are older patients with dysphagia, with or without chest pain, and normal oesophageal manometry, compared to similar cases aged 18-79 yrs. All included patients gave written, informed consent for their data to be used for research (Protocol HREC/13/SAC/215.13 Southern Adelaide Clinical Human Research Committee).

11.2.2 Study Procedures

Manometry studies were conducted as previously described (Chapter 4, page p. 96-111).

Provocative manoeuvres included multiple rapid swallowing (Fox et al. 2021). MRS were defined as indicating intact swallowing reserve function if $DCI_{MRS} > DCI_{liquid\ ave}$. For this study MRS was only assessed in the context of weak peristalsis, i.e., IOM/IEM. Impaired descending inhibition (Carlson et al. date) and LOS relaxation (Shaker et al. date) were also assessed during MRS.

For correlations (see below) the proximal oesophagus was assessed as the proximal contractile integral, defined as the sum of contractions above 20mmHg between the lower margin of the upper oesophageal sphincter and the peristaltic break. Correlations were calculated as the Pearson's correlation coefficient between oesophageal metrics and age. P-value of < 0.05 considered statistically significant.

11.3 Results

Table 11.1 Oesophageal Pressure-Flow Analysis Results								
	Liquids				Viscous			
	Young Controls (n=64)	Older Controls (n=30)	Patients (n=175)	Older Patients (n-91)	Young Controls (n=64)	Older Controls (n=30)	Patients (n=175)	Older Patients (n=91)
Age (average ± standard dev)	55±18	**86±4$^{\$\$\$}$**	50±14	**85±4$^{\$\$\$}$**	55±18	**86±4$^{\$\$\$}$**	50±14	**85±4$^{\$\$\$}$**
Oesophago-Gastric Junction (OGJ) Metrics								
OGJ Metrics								
IRP4 (mmHg)	8±1	**14±2$^{\$}$**	**13±2**	**13±2**	8±1	**18±3$^{\$}$**	**16±2**	**19±3**
OGJ-RP (mmHg)	25±2	**39±3$^{\$\$\$}$**	28±3	31±4	26±3	38±3	28±3	37±4
OGJ-CI (mmHg.s)	48±4	55±4	46±3	**65±9$^{\$}$**	48±6	58±4	46±5	**70±8$^{\$}$**
Oesophageal Pressure Topography								
DCI (mmHg.s.cm)	1198±125	**553±115$^{\$}$**	1831±698	1069±363	1066±207	598±223	1235±438	1272±412
DL (sec)	6.7±0.2	**8.2±0.4$^{\$\$}$**	6.9±0.3	7.6±0.5	7.1±0.2	7.8±0.6	7.2±0.3	8.5±0.9
PB (cm)	2±1	**5±1$^{\$\$}$**	**5±1**	**8±2**	1±1	4±1	**7±1**	**7±2**
Pressure Flow Metrics (Distension Pressures)								
DP Accommodation (mmHg)	0±1	**4±1$^{\$}$**	**3±2**	2±1	2±1	2±1	0±1	2±2
DP Transport (mmHg)	2±1	**6±1$^{\$}$**	**6±1**	**7±2**	5±1	6±1	3±1	9±3
DP Emptying (mmHg)	9±1	**18±2$^{\$\$\$}$**	**15±2**	**15±2**	12±1	**23±3$^{\$\$}$**	14±2	**18±2**
RP (mmHg.s)	6±1	4±1	**12±2**	4±4$^{\$}$	7±1	6±1	**16±3**	11±5
Timing								
SDL (sec)	3.6±0.2	4.5±0.4	4.8±0.4	**6.2±0.7$^{\$}$**	4.6±0.4	5.5±0.2	5.5±0.3	**7.3±0.7**
DCL (sec)	3.1±0.2	3.6±0.2	2.1±0.3	**1.4±0.5**	2.5±0.4	2.3±0.6	1.7±0.3	1.3±0.5
Bolus Transport								
IR	0.30±0.01	**0.43±0.03$^{\$}$**	**0.48±0.02**	**0.54±0.03**	0.39±0.02	**0.61±0.05$^{\$}$**	**0.51±0.02**	**0.64±0.02$^{\$\$}$**
BFT (sec)	3.6±0.2	5.4±1.8	1.6±0.2	2.0±0.3	3.0±0.3	2.8±0.4	**1.7±0.4**	2.0±0.4
Mucosal Integrity								
CSI	921±80	694±95	794±73	608±44				

Bold Text: P < 0.05 vs. Young Controls; **$^{\$}$ P < 0.05; $^{\$\$}$ P < 0.01; $^{\$\$\$}$ P < 0.001 vs. Young;** ***Average of 5 swallows per individual***

11.3.1 Comparing Younger and Older Patients (Metrics)

Average measurements for oesophageal metrics for younger and older patients are included as Table 11.1 (bolded values represent statistically significant differences from young controls). Specific differences within major and minor disorders of distal oesophageal motor disorders are described below (data in supplementary tables S11.1-S11.4 on page 214, at the end of this Chapter).

Older controls had reduced lower oesophageal sphincter relaxation and resting pressures, compared to young controls ($P < 0.05$). Contractility was also reduced in older, as compared to younger controls ($P < 0.05$). Distension pressures during accommodation ($P < 0.05$), transport ($P < 0.05$) and emptying ($P < 0.001$) were increased in older controls, while the impedance ratio was increased, indicating reduced bolus transport ($P < 0.05$) in older, as compared to young controls.

The oesophago-gastric junction contractile integral (OGJ-CI) was significantly increased in older, as compared to younger patients for both liquids, i.e., supine (OP 65±9 vs. P 46±3mmHg.s; $P < 0.05$) and viscous, i.e., upright (OP 70±8 vs. P 46±5mmHg.s; $P < 0.05$). Impedance ratio was increased for older patients during viscous swallows (OP 0.64±0.02 vs. P 0.51±0.02; $P < 0.01$).

11.3.2. Comparing Younger and Older Patients by Diagnosis

11.3.2.2 Achalasia

Achalasia subtypes were characterized by failed LOS relaxation (↑IRP4); for types I and II failed contractility; and for all subtypes, failed oesophageal bolus transport (↑IR). Qualitative pressure-flow analyses revealed that distension pressure increases, in Type II achalasia, related to oesophageal bolus presence rather the smooth muscle contraction (Table S11.1). There were no differences in the IRP4 (relaxation pressures) between achalasia subtypes,

young or older patients. OGJ resting pressures measured as a baseline resting pressure over three respiratory cycles, or OGJ contractile integrals were higher in older achalasia patients, as compared to younger achalasia patients ($P < 0.01$) and controls ($P < 0.001$). Type III achalasia had differing phenotypes in young and older patients: in young patients most Type III achalasia combined impaired LOS relaxation and multi-peaked hypercontractility; in older patients Type III achalasia patients had numerically increased IRP4 values, with preserved distal oesophageal contractility. Distension pressures were increased during transport in older Type III achalasia patients compared to younger patients ($P < 0.05$), and for viscous bolus also increased during oesophageal accommodation ($P < 0.05$), while the rate of pressure increase during oesophageal emptying (ramp pressures) were increased in younger Type III achalasia patients ($P < 0.001$).

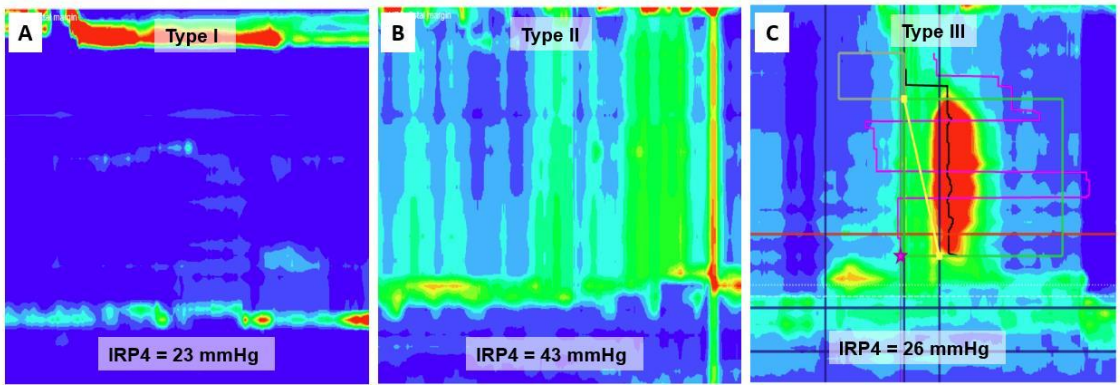


Figure 11.1 Older patients with types I – 80F (Fig 12.1A); II – 84M (Fig. 12.1B) and III achalasia – 88M (Fig. 12.1C).

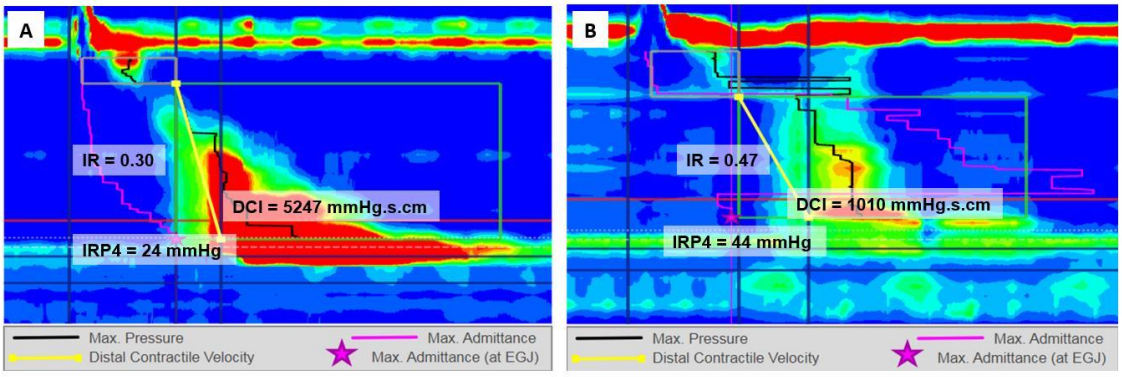


Figure 11.2 Type III achalasia in a 58M patient (Fig. 12.2A) and an 88M (Fig. 12.2B). While both studies meet criteria for Type III achalasia, contractility is markedly increased in the younger patient, approaching hypercontractility.

11.3.2.2 Oesophago-Gastric Junction Outflow Obstruction (OGJOO)

OGJOO is characterised by reduced LOS relaxation and intact contractility. During pressure-flow analyses emptying distention pressures and ramp pressures are increased in OGJOO. The OGJOO phenotype share some similarities with some older controls but differs through higher contractile integrals. There were no observed differences between younger and older patients with OGJOO.

11.3.2.3 Hypercontractile Oesophagus (HC)

Hypercontractile oesophagus was characterised by distal oesophageal hypercontractility. LOS relaxation was reduced in some older patients with HC, resulting in distal oesophageal bolus entrapment, associated with increases in emptying distention pressures and ramp pressures. Bolus transit was variable, but pressure flow analyses revealed prolonged but frequently successful trans-OGJ bolus transport. Distension pressures were also increased during transport in older patients HC, when compared to younger patients.

11.3.2.4 Distal oesophageal spasm (DOS)

DOS was characterised by a short distal latency. Time for oesophageal distension (the swallow to distension latency – SDL) was decreased in both younger and older patients with DES, in keeping with impaired inhibition. While LOS relaxation was measured as intact during liquid swallows, LOS resting, and relaxation pressures increased in DOS patients during viscous swallows. Following on from this, ramp pressure was markedly increased in patients with DOS.

11.3.2.5 Absent contractility and Ineffective Oesophageal Motility (IOM)

Absent contractility was characterised by absent distal, and in some cases also proximal oesophageal contractility. This was often associated with relatively low pressures at the OGJ and with poor bolus clearance. There were no observed differences for younger and older patients with absent contractility. IOM was characterised by weak oesophageal contractility

(defined as below 450mmHg.s.cm) and was also similar between younger and older patients. A description of multiple rapid swallowing (MRS) per age cohort in IEM patients below.

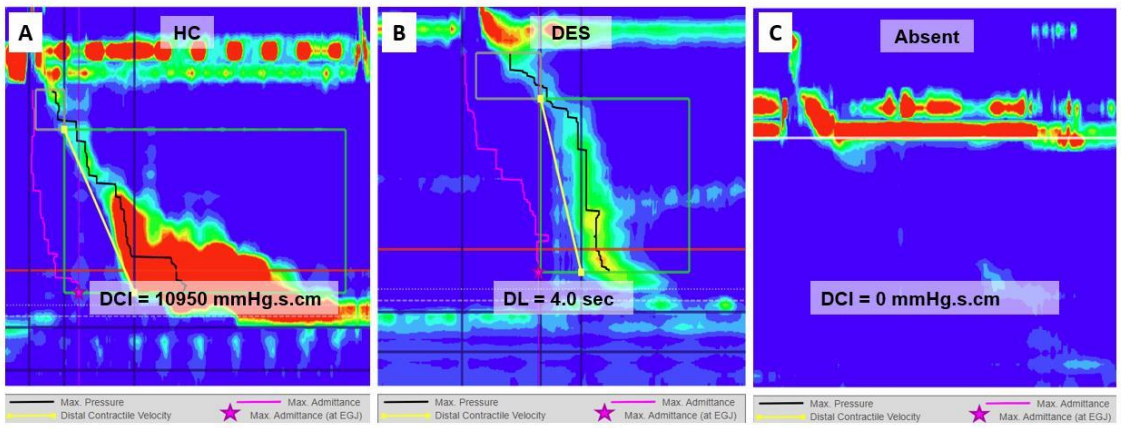


Figure 11.3 Older patients with hypercontractility – 87F (Fig 11.3A); distal oesophageal spasm – 80M (Fig. 11.3B) and absent contractility– 81M (Fig. 11.3C).

11.3.2.6 Non-obstructive Dysphagia (NOD)

NOD had similar pressure topography to controls but increased bolus retention. Older NOD patients had negative pressures during oesophageal phases. Bolus transport was impaired for both liquid and viscous consistencies in older NOD patients, however measured as statistically significant only for liquids.

11.3.3 Multiple rapid swallowing in IOM

MRS was successfully completed in n=131 patients (Table 12.7)

Table 11.2 MRS results per age cohort (% of total per age in brackets)

	Number Tested	Loss of Peristaltic Reserve Function n= (%)	Impaired DI n= (%)	Impaired LOS relaxation n = (%)
20-39 yrs	20	6 (30)	0 (0)	0 (0)
40-59 yrs	28	16 (57)	2 (7)	0 (0)
60-79 yrs	71	51 (72)	5 (7)	1 (1)
80 plus	12	11 (92)	2 (17)	1 (8)

When comparing patients aged 80 plus yrs with all those aged 20-59 yrs (i.e < 60 yrs), there was a greater loss of peristaltic reserve function in those 80 plus years of age (P < 0.01) (Figure 11.4).

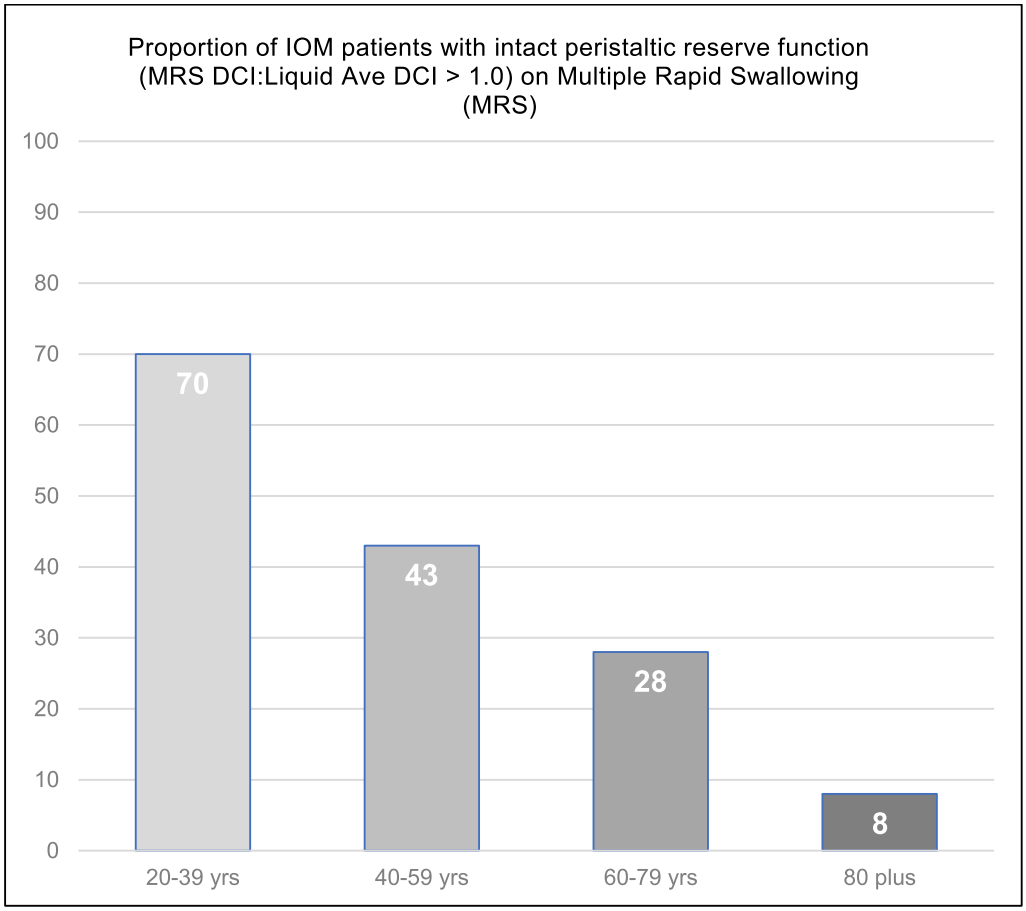


Figure 11.4 Proportion of IOM patients with intact peristaltic reserve (by age)

11.3.4 Correlation of Age with Oesophageal Metrics

Age correlated positively with impaired LOS relaxation (increasing IRP4), OGJ resting pressure and OGJ-CI. Age also correlated with reduced proximal oesophageal contractility and increased peristaltic breaks. Age correlated with increased distension pressures during all oesophageal phases but correlated negatively with ramp pressure during liquid swallows. Age correlated with a longer time from swallow onset to maximal distension (SDL).

Correlation of age with oesophageal metrics is shown in Table 11.3

Table 11.3 Correlation of Age with Oesophageal Metrics		
	Liquids	Viscous
Oesophago-Gastric Junction (OGJ) Metrics		
IRP4 (mmHg)	**0.223****	**0.285****
OGJ-RP (mmHg)	**0.263****	**0.314****
OGJ-CI (mmHg.s)	**0.257****	**0.288****
Oesophageal Pressure Topography		
PCI (mmHg.s.cm)	**-0.253****	**-0.339*****
DCI (mmHg.s.cm)	-0.120	0.005
DL (sec)	**0.299*****	0.151
PB (cm)	**0.256****	**0.216***
Pressure Flow Metrics		
DP Accommodation (mmHg)	**0.182***	0.070
DP Transport (mmHg)	**0.225****	**0.233***
DP Emptying (mmHg)	**0.321*****	**0.367*****
RP (mmHg.s)	**-0.188***	-0.085
Timing		
SDL (sec)	**0.293*****	**0.212***
DCL (sec)	-0.079	-0.080
Bolus Transport		
IR	**0.224****	**0.357*****
BFT (sec)	0.067	0.075

* P < 0.05; ** P < 0.01; *** P < 0.001

Age correlated with increased liquid and viscous bolus retention, as measured through IR. Additional results for disorders of distal oesophageal motor function are included as supplementary tables (supplementary tables S11.1-S11.4, page 214).

11.4 Discussion

This is the first study using high-resolution manometry with impedance and pressure-flow analysis to compare older patients with young patients, as well as with older (matched) and young controls.

Older patients differed from young patients through higher oesophago-gastric resting pressures, reduced proximal oesophageal contractility, and increased proximal bolus escape resulting in overall reduced bolus transport. Many of the changes observed in older patients were congruent with that seen in older controls, i.e., were age-related changes. Major disorders of distal oesophageal motor function were super-imposed on age-related changes. Peristaltic response to multiple rapid swallowing reduced markedly with age.

Metrics of oesophago-gastric revealed increased resting pressures and reduced relaxation in older persons. Such changes were previously observed in older healthy volunteers (Cock et al. 2017; Chapter 8) but in the patient cohort, especially those diagnosed with achalasia, LOS relaxation was less and OGJ-resting pressure greater. Such changes will be associated with increased flow resistance at the OGJ, needing a greater degree of intrabolus pressurisation to overcome (Nicosia & Brasseur 2002). It may also explain some of the differences in treatment response observed in older achalasia patients, such as a more enduring and greater response to injection of botulinum toxin observed (Heddle & Cock 2021), as such injection will reduce the effects of underlying tonic LOS contraction reducing the need for swallow-induced LOS relaxation to facilitate OGJ bolus flow.

Distension pressures were increased in type II achalasia compared to controls, and in older patients with type III achalasia. These changes relate to bolus-based luminal distension with poor bolus clearance in achalasia patients. This is congruent with the pathophysiology described previously by Park and colleagues, using intraluminal ultrasound (Park et al. 2018).

Distension pressures were also increased during oesophageal bolus transport of viscous bolus, in older patients with oesophageal hypercontractility. Changes in hypercontractility are congruent with distal oesophageal bolus entrapment and the initial component of the apparent contraction was often high intrabolus pressures rather than a lumen occlusive contraction. In other words, hypercontractility is induced by the trapped bolus in an attempt to facilitate bolus passage.

NOD patients appeared to represent multiple pathophysiologies. Sub-analysis of NOD is beyond the scope of this research program, but this observation suggests that a single unifying diagnosis seems unlikely. In older NOD patients, negative pressures during oesophageal accommodation may aid trans-UES bolus transport but remaining negative during further phases potentially suggest anatomical differences in the oesophagus and/or intrathoracic spaces may affect further bolus transport negatively, resulting in bolus retention. A significant increase in liquid bolus retention in older NOD patients is an interesting observation of unclear relevance.

Multiple rapid swallowing is used in ineffective oesophageal motility to determine oesophageal reserve function. This study demonstrated a progressive stepwise reduction in oesophageal peristaltic response with age (Figure 11.4). These observations are in keeping with the known reduction in cholinergic neurons in ageing (Meciano Filho 1995, Phillips 2003, Camilleri 2008) and caution against the overinterpretation of MRS response in predicting outcomes such as post-surgical dysphagia, in an older patient cohort. MRS has not been extensively assessed in older healthy volunteers, but some data collected within this research program suggest abnormal responses to rapid swallowing even in healthy older volunteers (see Biomechanical correlates of sequential drinking behavior in aging in Appendix B) which may be based on known upper oesophageal sphincter changes plusloss of oesophageal inhibition in some individuals.

The main limitation for this study were small numbers of older patients in some subgroups so that observations need to be interpreted with great caution and an inability to reliably demonstrate statistical differences in some subgroups. The analysis did potentially suggest that some oesophageal pressure topography phenotypes may have multiple pathophysiological mechanisms. The most obvious example of this is hypercontractility which is not infrequently found in association with a degree of OGJ flow restriction. Interestingly in many such cases hypercontractile responses result in ultimately successful but delayed distal oesophageal bolus clearance.

In conclusion, some differences were observed in older patients which would result in increasing OGJ flow resistance. Oesophageal pressure topography changes, representing the Chicago Classification, were superimposed on these observed changes and oesophageal bolus clearance was reduced in older patients, similarly to in older controls. Provocative maneouvres in older patients were in keeping with a significant reduction in peristaltic reserve function, in keeping with known age-related reduction in cholinergic neurons.

Supplementary Tables (Chapter 11)

Table S11.1 Oesophageal and Oesophago-Gastric Junction (OGJ) Metrics for Liquid Swallows (Major Disorders – OGJ, Hypercontractile, Spastic)

	Type I Ach		Type II Ach		Type III Ach		OGJOO		HC		DES	
	P	OP	P	OP	P	OP	P	OP	P	OP	P	OP
OGJ Metrics												
IRP4 (mmHg)	30±14***	23±2	28±5**	26±5	22±4*	18±3	39±4	36±7	4±1	16±3	15±4	11±1
OGJ-RP (mmHg)	32±7	60±17*	39±21	42±5	41±8	43±7	65±6	77±8	45±27	18±10	24±4	16±2
OGJ-CI (mmHg.s)	52±11	128±23***	59±24	88±10	61±6	104±17	132±12	175±11	66±28	42±29	48±12	32±2
Pressure Topography Metrics												
DCI (mmHg.s.cm)	67±57	58±54	1718±398	628±176	1017±469	1256±372	2674±499	3000±980	14185± 11565	**4237± 2734**	2975± 1963	6048±
DL (sec)	ND	ND	ND	ND	6.1±0.7	7.4±1.2	7.0±0.3	8.1±0.5	7.3±0.7	5.0±0.2	4.5±0.3*	3.4±
PB (cm)	ND	ND	ND	ND	3.5±1.0	1.5±0.9	2.5±0.8	2.9±1.4	0.1±0.1	2.3±1.6	1.2±0.7	0.2±0.2
Pressure Flow Metrics												
DP Accommodation (mmHg)	6±4	3±2	31±8***	13±2***	5±2	3±2	0±2	-1±4	6±2	-2±3	0±2	3±2
DP Transport (mmHg)	8±6	5±1	26±4***	21±6***	6±2	13±1	9±3	7±4	8±3	6±4	4±2	5±2
DP Emptying (mmHg)	27±8	23±4	33±5	21±7	24±3	22±4	38±2	32±5	12±4	15±1	14±2	13±4
RP (mmHg.s)	ND	ND	ND	ND	15±7***	3±2	21±4	23±13	19±9*	21±14*	24±11**	11±3
Timing Metrics												
SDL (sec)	ND	ND	ND	ND	5.1±1.0	6.4±0.8	5.1±0.3	6.6±0.4	4.6±0.1	3.2±0.2	2.8±0.2	3.0±0.4
DCL (sec)	ND	ND	ND	ND	0.9±0.6	1.0±1.9	1.8±0.2	3.0±0.9	2.6±0.7	1.7±0.4	2.0±0.4	1.7±0.7
Bolus Transit Metrics												
IR	0.71±0.03	0.66±0.08	0.83±0.06	0.79±0.06	0.45±0.03	0.55±0.04	0.47±0.03	0.56±0.03	0.46±0.02	0.51±0.08	0.33±0.04	0.32±0.02
BFT (sec)	0.6±0.6	1.3±1.2	1.4±0.8	0.9±0.8	1.6±0.3	3.3±0.4	2.3±0.3	3.0±0.9	4.8±2.6	2.2±0.9	1.4±0.5	1.1±0.5

**Average of five swallows per individual*

Table S11.2 Oesophageal and Oesophago-Gastric Junction (OGJ) Metrics for Liquid Swallows (Absent Contractility, IEM, Normal, Controls)

	Absent		IOM		Normal (NOD)		Controls	
	P	OP	P	OP	P	OP	P	OP
OGJ Metrics								
IRP4 (mmHg)	5±3	5±2	4±2	5±3	8±2	1±1	8±1	14±2
OGJ-RP (mmHg)	20±2	18±7	22±4	20±4	23±4	9±4	24±2	**39±3**
OGJ-CI (mmHg.s)	33±6	32±10	42±7	31±9	37±6	21±17	42±4	54±4
Pressure Topography Metrics								
DCI (mmHg.s.cm)	55±54	95±81	393±156	337±132	1509±383	504±357	1161±124	553±115
DL (sec)	ND	ND	7.2±0.3	7.2±1.1	7.3±0.4	**9.4±1.1**	6.6±0.2	**8.2±0.4**
PB (cm)	ND	ND	4.3±1.1	3.7±0.6	1.6±0.6	1.7±1.8	1.7±0.2	**5.3±0.9**
Pressure Flow Metrics								
DP Accommodation (mmHg)	-4±2	1±1	0±2	-2±2	-1±2	-2±3	0±1	**4±1**
DP Transport (mmHg)	0±2	2±1	1±1	2±2	-4±3	2±5	2±1	6±2
DP Emptying (mmHg)	7±2	10±3	9±2	10±2	-8±1	2±6	9±1	**17±2**
RP (mmHg.s)	ND	ND	9±1	8±2	12±4	4±1	4±1	4±1
Timing Metrics								
SDL (sec)	ND	ND	3.9±0.4	4.8±0.5	4.4±0.5	5.2±0.6	3.6±0.2	4.5±0.4
DCL (sec)	ND	ND	3.2±0.3	2.3±0.6	2.9±0.3	1.7±0.2	3.1±0.2	3.6±0.2
Bolus Transit Metrics								
IR	0.51±0.05	0.47±0.02	0.47±0.03	0.48±0.05	0.40±0.04	0.62±0.03***	0.30±0.01	**0.43±0.03**
BFT (sec)	0.5±0.3	1.6±1.3	2.2±0.3	2.6±0.9	1.6±0.4	0.4±0.2	3.6±0.2	5.5±1.8

**Average of five swallows per individual*

Table S11.3 Oesophageal and Oesophago-Gastric Junction (OGJ) Metrics for Viscous Swallows (Major Disorders – OGJ, Hypercontractile, Spastic)												
	Type I Achalasia		Type II Achalasia		Type III Achalasia		OGJOO		HC		DES	
	P	OP	P	OP	P	OP	P	OP	P	OP	P	OP
OGJ Metrics												
IRP4 (mmHg)	31±7	30±4	29±7	26±5	23±4	38±13	39±4	36±7	4±3	15±8	30±12	23±8
OGJ-RP (mmHg)	41±11	73±18	28±2	43±4	38±3	42±5	65±6	77±8	16±9	32±7	37±9	29±10
OGJ-CI (mmHg.s)	60±6	137±35	38±6	76±10	64±8	101±10	132±12	175±11	58±42	71±4	56±12	47±14
Pressure Topography Metrics												
DCI (mmHg.s.cm)	ND	ND	315±202	576±164	1611±677	2320±1127	2674±499	3000±980	10288 ±4941	6012 ±2079	2141± 1538	2044 ±1353
DL (sec)	ND	ND	ND	ND	6.3±0.5	6.7±0.9	7.0±0.3	8.1±0.5	7.9±0.5	9.2±0.9	5.1±0.2	4.5±0.3
PB (cm)	ND	ND	ND	ND	4.3±0.9	2.0±0.8	2.5±0.8	2.9±1.4	0.2±0.1	0.4±0.2	2.3±1.0	3.3±2.2
Pressure Flow Metrics												
DP Accommodation (mmHg)	0±4	2±3	10±2	12±2	-2±2	11±2	0±2	-1±4	7±2	2±1	2±3	-6±1
DP Transport (mmHg)	4±4	1±3	16±2	21±6	2±2	16±4	9±3	7±4	9±3	31±19	5±3	3±1
DP Emptying (mmHg)	21±4	31±4	27±3	23±7	23±4	22±4	38±2	32±5	8±6	22±7	21±5	21±5
RP (mmHg.s)	ND	ND	ND	ND	15±3	0±2	21±4	23±13	32±16	53±22	56±17	17±13
Timing Metrics												
SDL (sec)	ND	ND	ND	ND	4.3±0.6	6.5±3.2	5.1±0.3	6.6±0.4	6.1±0.6	7.8±1.5	3.9±0.3	3.4±0.3
DCL (sec)	ND	ND	ND	ND	1.9±0.5	1.8±2.5	1.8±0.2	3.0±0.9	1.7±0.2	1.4±0.6	1.1±0.1	1.1±0.1
Bolus Transit Metrics												
IR	0.80±0.02	0.68±0.04	0.77±0.03	0.84±0.05	0.55±0.04	0.71±0.05	0.47±0.03	0.56±0.03	0.46±0.05	0.56±0.09	0.60±0.06	0.61±0.04
BFT (sec)	0.0±0.2	1.1±0.3	1.0±0.9	0.9±0.8	1.6±0.1	3.1±0.7	2.3±0.3	3.0±0.9	2.2±1.1	3.8±2.4	0.9±0.5	3.0±2.1

**Average of five swallows per individual*

Table S11.4 Oesophageal and Oesophago-Gastric Junction (OGJ) Metrics for Viscous Swallows (Absent Contractility, IEM, Normal, Controls)								
	Absent		IOM		Normal (NOD)		Controls	
	P	OP	P	OP	P	OP	P	OP
OGJ Metrics								
IRP4 (mmHg)	7±5	7±3	9±3	8±4	7±2	2±1	8±1	17±3
OGJ-RP (mmHg)	11±3	18±10	31±6	25±7	19±5	18±2	25±3	38±4
OGJ-CI (mmHg.s)	14±4	38±20	48±11	39±15	29±6	21±4	48±6	57±4
Pressure Topography Metrics								
DCI (mmHg.s.cm)	26±14	35±14	440±160	387±92	893±194	436±432	1066±207	598±223
DL (sec)	ND	ND	7.4±0.4	7.2±0.5	7.8±0.5	7.7±0.5	7.1±0.2	7.8±0.6
PB (cm)	ND	ND	3.7±0.7	3.5±1.2	2.0±0.7	8.8±4.2	1.4±0.3	4.4±1.1
Pressure Flow Metrics								
DP Accommodation (mmHg)	-2±2	-4±2	-3±1	0±4	-1±2	-8±4	2±1	2±1
DP Transport (mmHg)	0±3	3±2	0±2	3±4	0±1	-8±2	5±1	6±1
DP Emptying (mmHg)	5±2	10±5	10±3	15±4	7±2	-3±5	12±1	22±3
RP (mmHg.s)	ND	ND	11±2	0±7	14±3	8±6	7±1	6±1
Timing Metrics								
SDL (sec)	ND	ND	5.4±0.3	5.3±0.7	5.9±0.6	5.6±0.3	4.6±0.4	5.5±0.7
DCL (sec)	ND	ND	2.1±0.3	1.8±1.1	1.9±0.2	1.9±0.2	2.5±0.4	2.2±0.6
Bolus Transit Metrics								
IR	0.61±0.04	0.66±0.08	0.48±0.02	0.35±0.06	0.47±0.02	0.57±0.04	0.39±0.02	0.60±0.05
BFT (sec)	0.8±0.4	1.4±0.7	2.7±0.8	2.7±0.8	1.3±0.3	0.6±0.6	3.0±0.3	2.8±0.4

**Average of five swallows per individual*

Part IV

Chapter 12 Summary of Results and Summative Discussion

12.1 Summary of Results

In addition to the in-depth discussions of findings in each individual chapter, this chapter briefly summarises and discusses the key findings from the research program presented in this thesis. These results are summarised below in Tables 12.1 and 12.2.

Table 12.1 Pharyngo-UOS Changes with Ageing (P-HRM-I)

Older persons (asymptomatic)	Older patients (symptomatic)
• Reduced UOS relaxation – UES IRP (chapters 5 and 8) • Reduced extent UOS opening – UES MaxAd (chapter 5 and 8) • Hypopharyngeal contractility increases then decreases (≥ 80 yrs) (chapter 8) • Swallow risk index (SRI) increases to levels associated with aspiration (≥ 85 yrs) (chapter 8)	*Additionally:* • Greater magnitude of reduced UOS distension (chapter 9) • Increased vallecular residue which may be perceived by patient to explain symptoms (chapter 9)

12.1.1 Key findings relating to the pharyngo-UOS region

Key findings relating to the pharyngo-UOS region are summarised in Table 12.1. Overall, in this region, findings from the older persons were in keeping with UOS dysfunction, whilst a previously reported increase in pharyngeal contractility (Shaker et al. 1993, Kern et al. 1999, Nativ-Zeltzer et al 2016) was not confirmed. Indeed, the findings from this program of research suggest that hypopharyngeal contractile vigour may increase, then become weaker, with

increasing age. The extent of UOS opening (Cock et al. 2016), was found to be reduced with age; this observation being most acute in patients who were reporting dysphagia symptoms. These patients also demonstrated increased amounts of pharyngeal residue, suggesting impaired swallowing efficacy. The global Swallow Risk Index (SRI), a composite measure previously associated with increased aspiration risk (Omari et al. 2011; Omari et al. 2014; Banyana et al. 2022), was also increased with age. In the oldest subgroup investigated (over 85 years of age), the SRI levels recorded were suggestive of impaired swallowing safety (Chapter 8). Thus, non-radiological P-HRM-I investigations could detect the progressive accumulation of swallowing dysfunctions associated with the aging process. The age of 85 years appears to represent a tipping point; whilst otherwise asymptomatic at the time of investigation. The over 85 year old's were on average at greater risk of swallowing failure compared to younger ages (20-79 yrs) and when compared their own baseline readings when they were 4-6 years younger (i.e., 80-85 yrs).

Table 12.2 Oesophago-OGJ Changes with Ageing (HRM-I)

Older persons (asymptomatic)	Older patients (symptomatic)
• Reduced LOS relaxation (Chapters 6,7 and 8) • Increasing length of peristaltic breaks (chapter 6) • Reducing oesophageal contractility (chapter 6 and 8) • Increased oesophageal distension pressures (chapter 8) • Reduced oesophageal bolus clearance progressing from viscous (IDDSI =4) ≥ 80 yrs to potentially including liquids (IDDSI = 0) ≥ 85 yrs (chapter 8)	*Additionally:* • Increased distension pressures in the oesophageal body during accommodation and emptying (chapters 10 and 11) • Increased oesophageal residue (chapters 10 and 11) *Increased diagnoses by main symptom:* • Dysphagia: DOS • Chest Pain: Weak/Absent (Reflux?) • Reflux: Achalasia (chapter 10)

12.1.2 Key findings relating to the oesophago-OGJ region

In the oesophago-OGJ region, findings from the older participants were in keeping with reduced contractile vigour of the oesophageal body and OGJ dysfunction (see Table 12.2 for a summary of key findings relating to this region). The observed dysmotility may have contributed to ineffective bolus transport and clearance. In the oldest subgroup investigated, (over 85 years of age), both liquid and viscous bolus transit were impaired, and adjunct findings of elevated bolus distension pressures during oesophageal emptying, were also seen. These findings are consistent with impaired luminal distensibility of the oesophageal body and OGJ as has been reported previously (Gregerson et al. 2008; Nicosia & Brasseur 2002). As with pharyngo-UOS function, the age of 85 years appears to represent a tipping point for the development of oesophageal motility disorders and associated bolus transit failure.

12.2 Discussion

This research program provides comprehensive data on pharyngo-oesophageal motor function in relation to age and was the first to extensively integrate intraluminal impedance into these assessments. At the time of commencement of this research program (2014), relatively few studies of pharyngeal or oesophageal manometry in ageing had been performed.

The P-HRM-I studies, described in chapters 5 and 8, in an older cohort, showed that pharyngeal contractility increased in those aged 60-79 yrs, a similar age cohort to that described in some previous studies (Shaker et al. 1993, Kern et al. 1999, Nativ-Zeltzer et al. 2016). In contrast with these past studies, increased pharyngeal pressures, which are proposed to represent a compensation for UOS restriction (Kern et al. 1999, Nativ-Zeltzer et al. 2016), were not present in the oldest participants. This novel finding, revealed through the inclusion of a sufficiently large sample of individuals aged 85 years and older, may have

important implications for understanding the effects of aging on swallowing function. It is noted that swallowing is more variable in ageing and by implication changes occur gradually as a shift in “range” so care should be taken when interpreting discreet “cut-offs” described.

Weaker contractile pressures may be due to altered length-tension properties of the muscle due to a larger pharyngeal space (Molfenter et al. 2015) or could be the result of pharyngeal sarcopenia. It is conceivable that these changes may have clinical relevance; for example, weaker hypopharyngeal contraction has been associated with aspiration risk (Omari et al 2011, O’Rourke et al. 2017, Bayona et al. 2022), especially when combined with UOS restriction (Omari et al. 2011). I would propose that these changes is swallowing function are measurable through derivation of the SRI, which therefore could serve as a non-specific marker for the loss of functional reserve.

Some of the most significant age-related differences were demonstrated through the use of impedance, which added several novel metrics that help to define UOS function. For example, one of these measures is maximum admittance (inverse impedance), which is a correlate of cross-sectional area (Omari et al 2012, Kim et al 2015) and which has been proposed as a non-specific marker of UOS dysfunction (Cock et al. no X 2016). UOS MaxAd did significantly decrease with ageing, over time and even more significantly in older patients; indeed, UOS MaxAd appeared to be one of the most reliable ways of distinguishing older patients from asymptomatic older persons (age matched controls) (chapter 9).

Another key impedance-dependent metric is hypopharyngeal IBP, a measure of UOS flow restriction (Pal et al. 2003, Omari et al . 2014), which can be easily measured based on the point of impedance-based maximal hypopharyngeal distension. While there was a numerical increase in hypopharyngeal IBP in the group ≥ 80 years, this increase was not statistically significant, likely due to failure of augmentation of posterior tongue and pharyngeal contractility, shown in this research program and by others (Jones & Corelli 2021). In the

context of relatively reduced contractility, UOS IBP becomes less reliable as a marker of UOS-dysfunction (Szczesniak et al. 2018).

Studies in this research program have contributed significantly to the development of P-HRM-I methodologies that have refined our ability to study oropharyngeal dysphagia, (Omari, Cock, et al. 2022) and which we have been recently synthesised into a clinically useful schema for UOS dysfunction (Figure 12.1). In short, UOS dysfunction on P-HRM-I is defined by a combination of pressurization patterns and increased UOS IRP (non-relaxation) plus either increased hypopharyngeal IBP or decreased extent of UOS distension (UOS MaxAd). The important consideration here is to base the diagnosis of a UOS disorder on *multiple* adjunct findings, in the hope of reducing the chances of a false-positive result. This will hopefully avoid the negative experience encountered in oesophageal physiological assessment, where OGJOO was being over diagnosed because it was based on a single metric (i.e., OGJ IRP4s).

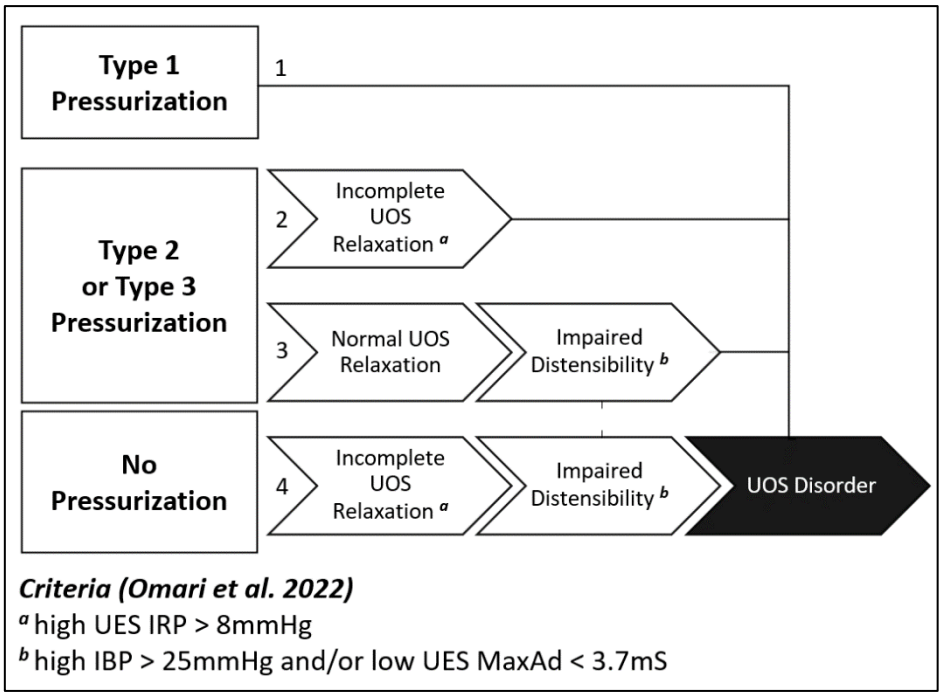


Fig 12.1 Schema for P-HRM-I assessed UOS Dysfunction

This research program also includes the first description of the use of HRM-I and pressure-flow to study oesophageal function in older persons. The use of the Chicago Classification (CC) of motor disorders of the distal oesophagus, based on oesophageal pressure topography, is now well established for the interpretation of distal oesophageal motility studies. However, the CC lacks any assessment of the proximal oesophagus and also does not include metrics related to the interpretation of impedance data (impedance-based clearance is qualitatively assessed). In addition to adding these analyses with HRM-I, analysis of distension pressures and their relation to oesophageal clearance and symptoms were assessed (chapter 11).

Proximal oesophageal contractility was reduced in older persons and patients, while proximal bolus retention occurred more often in this setting. Non-specific markers of pharyngo-UOS dysfunction, SRI and UOS MaxAd were both abnormal in asymptomatic older persons with failed oesophageal bolus clearance (chapter 6, page 137). While it makes sense that downstream events depend on pharyngeal bolus delivery, there has been very limited exploration of this aspect (Omari et al. 2012), and this interrelationship between pharyngeal and oesophageal function remains worthy of further, focused exploration.

HRM-I studies in asymptomatic older persons (chapters 6 and 7) confirmed an increase in OGJ IRP, which had previously been described (Besanko et al. 2014, Jung et al 2015). The further use of pressure-flow analysis and a pressure-flow matrix demonstrated that impaired oesophageal bolus transit in older persons, previously shown on radiology (Soergel et al 1964, Zobralske et al. 1964, Jou et al. 2009), related both proximal and distal oesophageal bolus retention, which was associated with increases in distension pressures. Bolus retention was markedly increased for viscous over liquid consistencies but progressed to involving both consistencies in older persons over 85 years of age (chapter 8). Increased distension pressures, in this context, may occur as a result of distal flow restriction (Nicosia & Brasseur 2002), a stiffer oesophagus wall (Gregerson et al. 2008), and the presence of the bolus. During

clinical radiology, abnormal bolus clearance in older persons needs to be interpreted with caution, as it appears to be a frequent observation of questionable clinical significance. In my view, IR serves as quantifiable and comparable measurement of residue, during O-HRM-I.

The study of symptomatic older patients (chapter 10), with a focus on separate and comparative analysis of those age ≥ 80 years, represents the largest comprehensive study of HRM-I in older patients. Past studies have reported inconsistent findings and have not reliably demonstrated an increase in major disorders of distal oesophageal motility in older persons. A study by Djiinbachian and colleagues (Djiinbachian et al. 2021) did correlate age to LOS IRP but did not consider or demonstrate diagnostic changes resulting from this observation. HRM studies by Nakato et al. (Nakato et al. 2017) and Shim et al. (Shim et al 2017) also did not demonstrate increased number of diagnoses or even altered metrics in older patients but used an age cut-off of 65 yrs. As such, this program of research contributed important new, clinically relevant information to the interpretation of HRM-I in older patients (≥ 80 yrs).

Another important novel finding of this research program was the description of a loss of peristaltic reserve function in older patients. The proportion of intact peristaltic reserve function in older patients (≥ 80 years) with ineffective oesophageal motility was only 8%, compared to 70% in those aged 20-39 years (chapter 11). While a known loss of enteric excitatory neurons (Johnson et al. 1998, Cowen et al. 2000, Phillips et al. 2003, Wade & Cohen 2004, Camilleri et al. 2008, Salles 2009) likely underlies this observation, this novel finding has important implications for interpreting the result of multiple rapid swallowing or other provocative manoeuvres in older patients.

Table 2.3 (page 35) defined impaired and failed swallowing function throughout the pharyngeal-UOS and oesophageal-OGJ regions, based on available criteria. Conceptually reduced function is considered *impaired* when still partly intact but *failed* when aspiration occurred during pharyngeal swallowing, or oesophageal bolus clearance failed. Studies in this

research program identify SRI as metric to measure pharyngo-UOS function, and IR as a metric for oesophago-OGJ function.

Figure 2.13 (below) was proposed as a representation of functional decline with ageing.

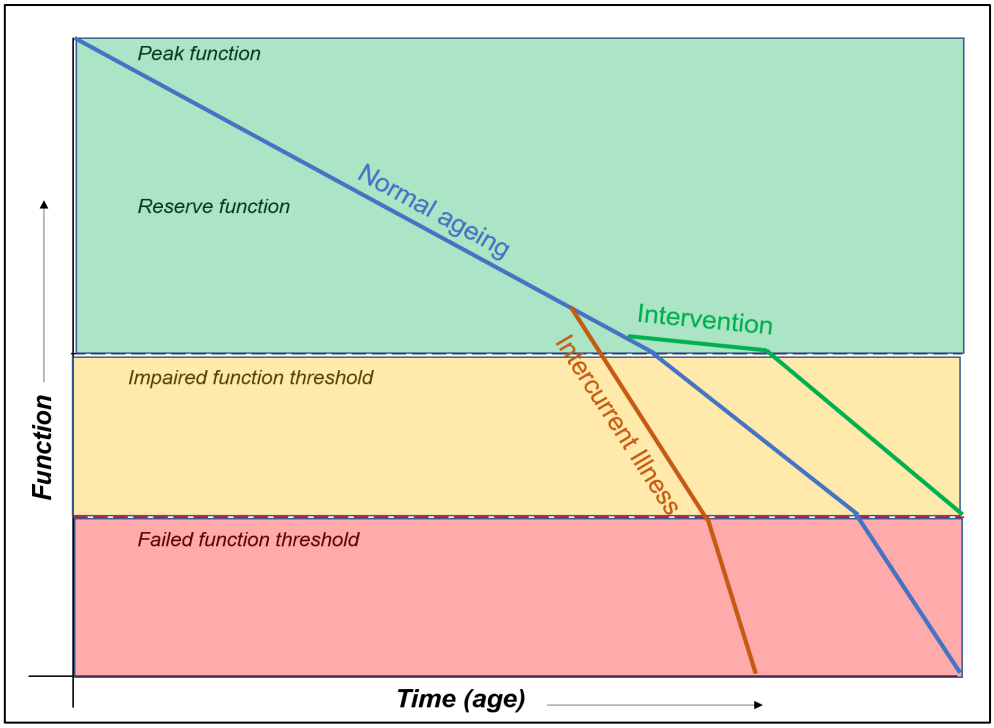


Figure 2.13 Functional decline (y-axis) over time (x-axis).

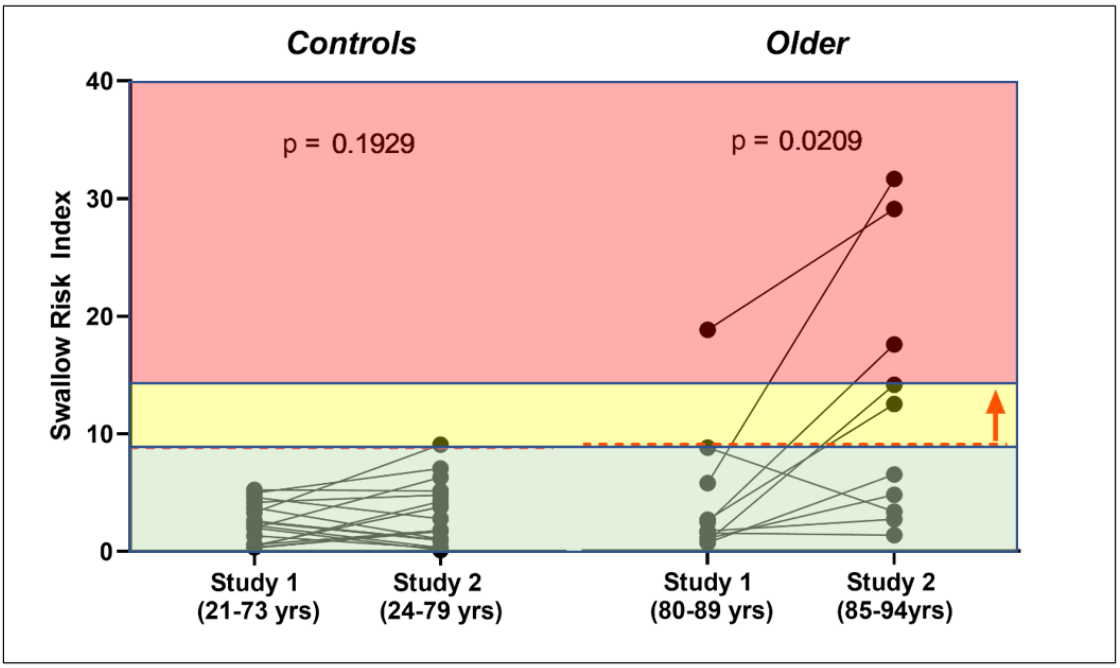


Figure 12.2 Application of the concept of functional decline to a representation of the swallow risk index (SRI) in older persons studied on two separate occasions 4-6 years apart (see text).

This model of functional decline or impaired reserve function can conceptually be applied to figure 8.2 (chapter 8, p168) (figure 12.2) but with an increase in SRI over time representing progression from function (green) to dysfunction: impaired (yellow) and failed function (red).

I am proposing this model using SRI to for application in assessing age-related swallowing function, with an analogous model using IR for differing consistencies in the oesophagus. Other swallowing assessments should be tested against this model in individuals and groups, to develop alternative forms of subjective and objective testing of swallowing function.

The systematic investigation of changes in pharyngeal and oesophageal high-resolution manometry with impedance (HRM-I) in older persons (≥ 80 yrs) presented in this thesis has made significant contributions to our understanding of age-related swallowing function and dysfunction. It addresses a major deficit in the existing literature, which is lacking studies of the older old cohort of aged individuals and demonstrates differences in this group, even from those aged between 60 and 80 yrs. Much of this program has also served to further develop P-HRM-I methodologies for clinical use, as described in Chapter 9 and in Omari, Cock et al. 2022. (Omari et al. 2022). The research has also revealed intriguing interrelationships between pharyngeal and oesophageal motility and establishes a baseline for further studies of swallowing interventions to improve age-related swallowing dysfunction.

Chapter 13 Conclusion & Future Directions

The program of research presented in this thesis evaluated pharyngeal and oesophageal swallowing biomechanics, using P-HRM-I, in advanced age. Overall, pharyngo-UOS biomechanical changes observed in older persons and patients (≥ 80 yrs) were in keeping with UOS dysfunction, in that the extent of UOS distension/opening reduced gradually over the lifespan (chapters 5 and 8). UOS dysfunction was initially compensated for by increased pharyngeal contractility, but such increase was not maintained in the oldest participants. Beyond 85 yrs of age, biomechanical changes/UOS dysfunction were severe enough to constitute functional failure, manifest as increased aspiration risk (chapter 8). Novel P-HRM-I metrics such as UOS MaxAd and swallow risk index (SRI) were most altered and could serve as non-specific markers of, and/or screening tests for, age-related swallowing dysfunction.

The use of impedance during P-HRM-I adds the ability to non-radiologically detect early arrival of the bolus, a lack of bolus-based distension (opening) of the UOS, and lack of bolus departure (i.e., residue), which are all critical components distinguishing OPD patients from controls (chapter 9). In the older oropharyngeal dysphagia patients, UOS dysfunction predominated (chapter 9). In a patient cohort, as compared to community dwelling healthy older persons, more invasive interventions targeting the UOS (dilatation or even myotomy e.g., cricopharyngeal per-oral endoscopic myotomy) could be considered earlier than it would normally be, guided by P-HRM-I investigation.

While subjective tests of swallowing function such as questionnaires may be unreliable in older persons, some findings in this research program also suggest caution in interpreting biomechanically based objective testing such as the water swallow test (WST). (Also see Cock et al. 2021 – Biomechanical correlates of sequential swallowing in Appendix B). Biomechanical assessments such as P-HRM-I could help develop interventions (e.g., novel fluid biomechanics) to guide dietary strategies in nursing homes. Generalisability and acceptability

of interventions developed based on such an approach would require further study. Furthermore, programs focusing on swallowing exercises targeting UOS opening, e.g., the head lift/Shaker exercise (Shaker et al. 1997, Logemann et al. 2009) could be designed to target those at greatest risk of aspiration, based on assessments developed to correlate with SRI. Such an approach should be trialled in a randomised, sham-controlled fashion in the nursing home setting.

Oesophageal abnormalities in older persons (≥ 80 yrs) were characterised by reduced contractility and LOS relaxation, accompanied by reduced and failed bolus clearance. Underlying mechanisms may relate to age-related neurodegeneration involving sensory as well as excitatory and inhibitory motor neurons. An interrelationship between pharyngeal and oesophageal swallowing function was demonstrated, which is worthy of further, focused investigation (also see Cock et al. unpublished paper in Appendix C). It would be of interest, for example, to test whether programs focusing on posterior tongue function (Oh 2022) may improve oesophageal swallowing. A pilot study had demonstrated manoeuvres such as effortful swallowing and Mendelsohn manoeuvre may improve oesophageal distal oesophageal contractility (O'Rourke et al. 2014).

The genesis of symptoms in some older patients presenting with dysphagia or unexplained chest pain remains unclear and a topic of further investigation. The use of HRM-I with pressure-flow analysis may help elucidate the cause of symptoms in some individuals (chapter 11).

This research program set out to assess swallowing function in ageing, using HRM-I and adds to our understanding of the biomechanics underlying swallowing dysfunction in ageing. Novel metrics such as SRI and IR were shown to be able to assess swallowing function reserve in ageing and provide objective measurements for interventional studies (chapters 8 and 12)

It is my vision that the findings outlined in this thesis will be useful in designing future preventative and rehabilitative intervention studies, which ultimately, will be able to not only improve quantity but importantly also quality of life in older persons.

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Appendix A: Published Studies Included in Thesis

1. **Cock C**, Omari T. Systematic Review of Pharyngeal and Esophageal Manometry in Healthy or Dysphagic Older Persons (>60 years). Geriatrics (Basel). 2018 Oct 5;3(4):67. doi: 10.3390/geriatrics3040067. (***Chapter 2.3***)

2. Omari TI, Kritas S, **Cock C**, Besanko L, Burgstad C, Thompson A, Rommel N, Heddle R, Fraser RJ. Swallowing dysfunction in healthy older people using pharyngeal pressure-flow analysis. Neurogastroenterol Motil 2014; 26: 59-68 ***(Chapter 5)***

3. **Cock C**, Besanko L, Kritas S, Burgstad CM, Thompson A, Heddle R, Fraser RJ, Omari TI. Impaired bolus clearance in asymptomatic older adults during high-resolution impedance manometry. Neurogastroenterol Motil 2016; 28: 1890-1901 ***(Chapter 6)***

4. **Cock C**, Besanko LK, Burgstad CM, Thompson A, Kritas S, Heddle R, Fraser RJL, Omari TI. Age-related impairment of esophagogastric junction relaxation and bolus flow time. World J Gastroenterol 2017; 23(15):2785-2794 ***(Chapter 7)***

5. Omari T, **Cock C**, Wu P, Szczesniak MM, Schar M, Tack J, Rommel N. Using high resolution manometry impedance to diagnose upper esophageal sphincter and pharyngeal motor disorders. Neurogastroenterol Motil. 2022 Sep 19:e14461. doi: 10.1111/nmo.14461. Epub ahead of print. PMID: 36121685. ***(Chapter 9)***

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CO-AUTHORSHIP APPROVALS FOR HDR THESIS FOR EXAMINATIONS

In accordance with Clause 5, 7 and 8 in the HDR Thesis Rules, a student must sign a declaration that the thesis does not contain any material previously published or written by another person except where due reference is made in the text or footnotes. There can be no exception to this rule.

a. Publications or significant sections of publications (whether accepted, submitted or in manuscript form) arising out of work conducted during candidature may be included in the body of the thesis, or submitted as additional evidence as an appendix, on the following conditions:
   I. they contribute to the overall theme of the work, are conceptually linked to the chapters before and after, and follow a logical sequence
   II. they are formatted in the same way as the other chapters (i.e. not presented as reprints unless as an appendix), whether included as separate chapters or integrated into chapters
   III. they are in the same typeface as the rest of the thesis (except for reprints included as an appendix)
   IV. published and unpublished sections of a chapter are clearly differentiated with appropriate referencing or footnotes, and
   V. unnecessary repetition in the general introduction and conclusion, and the introductions and conclusions of each published chapter, is avoided.

b. Multi-author papers may be included within a thesis, provided:
   I. the student is the primary author
   II. there is a clear statement in prose for each publication at the front of each chapter, recording the percentage contribution of each author to the paper, from conceptualisation to realisation and documentation.
   III. The publication adheres to Flinders Research Publication, Authorship and Peer Review Policy, and
   IV. each of the other authors provides permission for use of their work to be included in the thesis on the Submission of Thesis Form below.

c. Papers where the student is not the primary author may be included within a thesis if a clear justification for the paper's inclusion is provided, including the circumstances relating to production of the paper and the student's position in the list of authors. However, it is preferable to include such papers as appendices, rather than in the main body of the thesis.

STUDENT DETAILS

Student Name	Charles Cock
Student ID	2143609
College	College of Medicine and Public Health
Degree	PhD
Title of Thesis	High-resolution manometry with impedance for the assessment of age-related dysphagia

PUBLICATION 1

This section is to be completed by the student and co-authors. If there are more than four co-authors (student plus 3 others), only the three co-authors with the most significant contributions are required to sign below.

Please note: A copy of this page will be provided to the Examiners.

Full Publication Details	Cock C, Omari T. Systematic Review of Pharyngeal and Esophageal Manometry in Healthy or Dysphagic Older Persons (>60 years). Geriatrics (Basel). 2018 Oct 5;3(4):67. doi: 10.3390/geriatrics3040067. PMID: 31011102; PMCID: PMC6371098.
Section of thesis where publication is referred to	Chapter 2.3

Student's contribution to the publication

80	%	Research design
80	%	Data collection and analysis
80	%	Writing and editing

Outline your (the student's) contribution to the publication:

Conceived review in conjunction with supervisor. Researched methodology for a Systemic Review. Researched methodology related to rating evidence (GRADE system).Conducted literature search. Decided in conjunction with supervisor which studies to include in review. Tabulated and summarised evidence from different studies. Wrote discussion in conjunction with supervisor. Note the chapter included in thesis removed studies conducted as part of this thesis and rewrote discussion.

APPROVALS

By signing the section below, you confirm that the details above are an accurate record of the students contribution to the work.

Name of Co-Author 1 Prof Taher Omari Signed  Date 13/10/22

Name of Co-Author 2 _____ Signed _____ Date _____

Name of Co-Author 3 _____ Signed _____ Date _____

PUBLICATION 3

This section is to be completed by the student and co-authors. If there are more than four co-authors (student plus 3 others), only the three co-authors with the most significant contributions are required to sign below.

Please note: A copy of this page will be provided to the Examiners.

Full Publication Details	Cock C, Besanko L, Kritas S, Burgstad CM, Thompson A, Heddle R, Fraser RJ, Omari TI. Impaired bolus clearance in asymptomatic older adults during high-resolution impedance manometry. Neurogastroenterol Motil 2016; 28: 1890-1901
Section of thesis where publication is referred to	Chapter 6

Student's contribution to the publication

70	%	Research design
80	%	Data collection and analysis
80	%	Writing and editing

Outline your (the student's) contribution to the publication:

Conceived study in conjunction with supervisors. Contributed significantly to collecting data (recruitment and performing studies). Analysed data using Aimplot (Matlab software). Significant proportion of writing and editing of manuscript. Submitted for publication.

APPROVALS

By signing the section below, you confirm that the details above are an accurate record of the students contribution to the work.

Name of Co-Author 1	Prof Taher Omari	Signed		Date	13/10/22
Name of Co-Author 2	Prof Robert Fraser	Signed		Date	12/10/22.
Name of Co-Author 3	Dr Richard Heddle	Signed		Date	12/10/22

PUBLICATION 2

This section is to be completed by the student and co-authors. If there are more than four co-authors (student plus 3 others), only the three co-authors with the most significant contributions are required to sign below.

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Full Publication Details	Omari TI, Kritas S, Cock C, Besanko L, Burgstad C, Thompson A, Rommel N, Heddle R, Fraser RJ. Swallowing dysfunction in healthy older people using pharyngeal pressure-flow analysis. Neurogastroenterol Motil 2014; 26: 59-68
Section of thesis where publication is referred to	Chapter 5* ** Chapter 5 includes re-analysis and rewrite of data form this publication*

Student's contribution to the publication

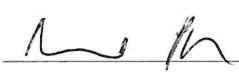
50	%	Research design
50	%	Data collection and analysis
30	%	Writing and editing

Outline your (the student's) contribution to the publication:

Conceived study in conjunction with supervisors. Contributed significantly to collecting data (recruitment and performing studies). Analysed data using Aimplot (Matlab software). Some writing and editing of manuscript. The version included as chapter 5 is a complete reworking of the data (re-analysis using Swallowgateway.com) which is much more substantially (80%) the students work.

APPROVALS

By signing the section below, you confirm that the details above are an accurate record of the students contribution to the work.

Name of Co-Author 1	Prof Taher Omari	Signed		Date	13/10/22
Name of Co-Author 2	Prof Robert Fraser	Signed		Date	12/10/22
Name of Co-Author 3	Dr Richard Heddle	Signed		Date	12/10/22

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Full Publication Details	Cock C, Besanko LK, Burgstad CM, Thompson A, Kritas S, Heddle R, Fraser RJL, Omari TI. Age-related impairment of esophagogastric junction relaxation and bolus flow time. World J Gastroenterol 2017; 23(15):2785-2794
Section of thesis where publication is referred to	Chapter 7

Student's contribution to the publication

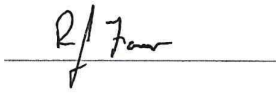
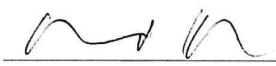
80	%	Research design
80	%	Data collection and analysis
80	%	Writing and editing

Outline your (the student's) contribution to the publication:

Conceived study in conjunction with supervisors. Contributed significantly to collecting data (recruitment and performing studies). Analysed data using Aimplot (Matlab software) and using metrics on manometry software. Significant proportion of writing and editing of manuscript. Submitted for publication.

APPROVALS

By signing the section below, you confirm that the details above are an accurate record of the students contribution to the work.

Name of Co-Author 1	Prof Taher Omari	Signed		Date	13/10/22
Name of Co-Author 2	Prof Robert Fraser	Signed		Date	12/10/22
Name of Co-Author 3	Dr Richard Heddle	Signed		Date	12/10/22

PUBLICATION 5

This section is to be completed by the student and co-authors. If there are more than four co-authors (student plus 3 others), only the three co-authors with the most significant contributions are required to sign below.

Please note: A copy of this page will be provided to the Examiners.

Full Publication Details	Omari T, Cock C, Wu P, Szczesniak MM, Schar M, Tack J, Rommel N. Using high resolution manometry impedance to diagnose upper esophageal sphincter and pharyngeal motor disorders. Neurogastroenterol Motil. 2022 Sep 19:e14461.
Section of thesis where publication is referred to	Chapter 9* **Data contained in Chapter 9 consists of a subset of data in older patients (> 80 yrs)*

Student's contribution to the publication

33.3	%	Research design
33.3	%	Data collection and analysis
33.3	%	Writing and editing

Outline your (the student's) contribution to the publication:

Conceived study in conjunction with supervisors and with input from Prof Rommel. Contributed to the collection of clinical data for analysis. Contributed significantly to data analysis (Swallowgateway.com). Contributed to writing and editing of manuscript. Chapter 9 uses data from the included study but analyses are limited to participants > 80 yrs. Re-analysing data and writing chapter 9 was substantially the students work (80%)

APPROVALS

By signing the section below, you confirm that the details above are an accurate record of the students contribution to the work.

Name of Co-Author 1	Prof Taher Omari	Signed		Date	13/10/22
Name of Co-Author 2	Prof Nathalie Rommel	Signed		Date	
Name of Co-Author 3	Dr Peter Wu	Signed		Date	

CO-AUTHORSHIP APPROVALS FOR HDR THESIS EXAMINATION

PUBLICATION 5

This section is to be completed by the student and co-authors. If there are more than four co-authors (student plus 3 others), only the three co-authors with the most significant contributions are required to sign below.

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Full Publication Details	Omari T, Cock C, Wu P, Szczesniak MM, Schar M, Tack J, Rommel N. Using high resolution manometry impedance to diagnose upper esophageal sphincter and pharyngeal motor disorders. Neurogastroenterol Motil. 2022 Sep 19:e14461.
Section of thesis where publication is referred to	Chapter 9* *Data contained in Chapter 9 consists of a subset of data in older patients (> 80 yrs)*

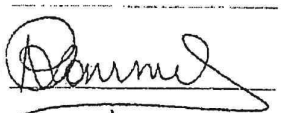
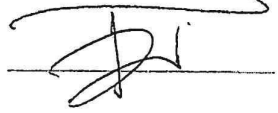
Student's contribution to the publication	33.3	%	Research design
	33.3	%	Data collection and analysis
	33.3	%	Writing and editing

Outline your (the student's) contribution to the publication:

Conceived study in conjunction with supervisors and with input from Prof Rommel. Contributed to the collection of clinical data for analysis. Contributed significantly to data analysis (Swallowgateway.com). Contributed to writing and editing of manuscript. Chapter 9 uses data from the included study but analyses are limited to participants > 80 yrs. Re-analysing data and writing chapter 9 was substantially the students work (80%)

APPROVALS

By signing the section below, you confirm that the details above are an accurate record of the students contribution to the work.

Name of Co-Author 1	Prof Taher Omari	Signed		Date	
Name of Co-Author 2	Prof Nathalie Rommel	Signed		Date	11.10.2022
Name of Co-Author 3	Dr Peter Wu	Signed		Date	12.Oct.2022

Appendix B: Published Studies Related to Thesis

1. **Cock C**, Omari T. Diagnosis of Swallowing Disorders: How We Interpret Pharyngeal Manometry. Curr Gastroenterol Rep. 2017 Mar;19(3):11. doi: 10.1007/s11894-017-0552-2. (Chapter 4)

2. **Cock C**, Besanko L, Kritas S, Burgstad CM, Thompson A, Heddle R, Fraser RJ, Omari TI. Maximum upper esophageal sphincter (UES) admittance: a non-specific marker of UES dysfunction. Neurogastroenterol Motil. 2016 Feb;28(2):225-33. doi: 10.1111/nmo.12714. Epub 2015 Nov 6.

3. **Cock C**, Jones CA, Hammer MJ, Omari TI, McCulloch TM. Modulation of Upper Esophageal Sphincter (UES) Relaxation and Opening During Volume Swallowing. Dysphagia. 2017 Apr;32(2):216-224. doi: 10.1007/s00455-016-9744-4. Epub 2016 Aug 17.

4. **Cock C**, Leibbrandt RE, Dinning PG, Costa MC, Wiklendt L, Omari TI. Changes in specific esophageal neuromechanical wall states are associated with conscious awareness of a solid swallowed bolus in healthy subjects. Am J Physiol Gastrointest Liver Physiol. 2020 May 1;318(5):G946-G954. doi: 10.1152/ajpgi.00235.2019. Epub 2020 Apr 13.

5. **Cock C**, Omari TI, Burgstad CM, Thompson A, Doeltgen SH. Biomechanical correlates of sequential drinking behavior in aging. Neurogastroenterol Motil. 2021 Jan;33(1):e13945. doi: 10.1111/nmo.13945. Epub 2020 Jul 14.

6. Omari T, Rommel N, Jan T, Szczesniak M, Wu P, Schar M, Doeltgen S, **Cock C**. Transient hypopharyngeal intrabolus pressurization patterns: Clinically relevant or normal variant? Neurogastroenterol Motil. 2022 Jun;34(6):e14276. doi: 10.1111/nmo.14276. Epub 2021 Oct 4.

Appendix C: Additional Unpublished Material

1. **Cock C,** Schar M, Omari T. Aimplot-Derived Biomechanical Measures: Which ones Differentiate Normal from Disordered Swallowing? – Oral Presentation Dysphagia Research Society Meeting - March 2018, Baltimore, Maryland, USA

2. **Cock C,** Doeltgen S, Schar M, Burgstad C, Thompson A, Fraser R, Omari T. Volume Effects on Upper Esophageal Sphincter Opening in Ageing.– Oral Presentation Dysphagia Research Society Meeting - March 2018, Baltimore, Maryland, USA

3. **Cock C,** Singendonk MM, Greig J, Stocks A, Mok D, Schar M, Ferris L, Doeltgen S, Burgstad C, Thompson A, Barnes A, Heddle R, Fraser RJL, Rommel N, Omari T. Failed Esophageal Bolus Clearance Occurs Commonly in Oropharyngeal Dysphagia, Irrespective of Chicago Diagnosis

Session 4 - Directions in Diagnostics
26th Annual DRS Meeting, March 15 - 17, 2018, Baltimore, MD

AIMplot-Derived Biomechanical Measures:
Which Ones Differentiate Normal from Disordered Swallowing?

Cock, Charles[2]; Schar, Mistyka[2]; Omari, Taher[1]
1. Human Physiology, Flinders University, Adelaide, SA, Australia.
2. Flinders Medical Centre, Adelaide, SA, Australia.

AIM-plot pressure-flow analysis derives biomechanical measures of swallowing function based on high-resolution impedance-manometry (HRIM).

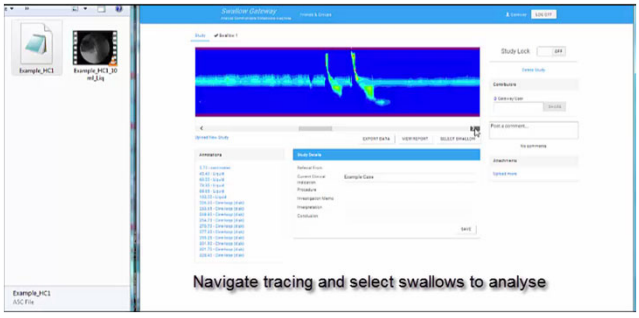
- **Contractility**
- **Flow Latency**
- **Intrabolus Pressure**
- **Bolus Presence**

Study Aim

To determine which AIMplot variables could differentiate patients from controls.

Methods

Asymptomatic controls
N = 10, 24–33years
Dysphagia patients within 3 subgroups.
Group 1: Dysphagia following UPPP sleep apnea surgery
N= 5, 48-63years
Group 2: Dysphagia following head & neck cancer treatment
N=5, 63-75 years
Group 3: Extubated ICU patients commencing oral feeding
N = 15, 50-78years.
Standardized Swallow Protocol
5 &10ml volumes
thin & extremely thick fluid consistency (IDDSI 0 and 4).



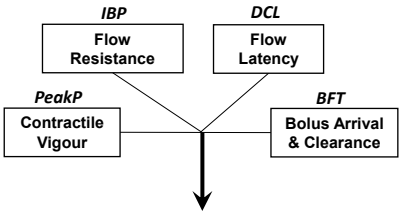
Studies were uploaded to the AIMplot open access website *swallowgateway.com*
A global Swallow Risk Index (SRI) and 14 individual swallow variables were determined.
Results (overall and per-subgroup) were compared.
The ability to differentiate Controls from Patients was determined using ROC (null hypothesis AUC = 0.5).

Swallow Function Metrics

	Metric	Abbreviation
Global Pharyngeal Function	Swallow Risk Index	*SRI*
Pressure Generation / Contractility	UES Basal Pressure	*UES BP*
	Velopharyngeal to Tongue Base Integral	*VTI*
	Hypopharyngeal Contractile Integral	*HPCI*
	UES Peak Pressure	*UES Peak P*
	UES Contractile Integral	*UESCI*
	Proximal Esophageal Contractile Integral	*PCI*
Bolus Distension Pressure / Distension Diameter	UES Maximum Admittance	*UES Max Adm*
	UES Integrated Relaxation Pressure	*UES IRP*
	Hypopharyngeal Intrabolus Pressure	*IBP*
Flow Timing/ Bolus Presence	UES Open Time	*UES Open T*
	Bolus Presence Time	*BPT*
	Distension Contraction Latency	*DCL*

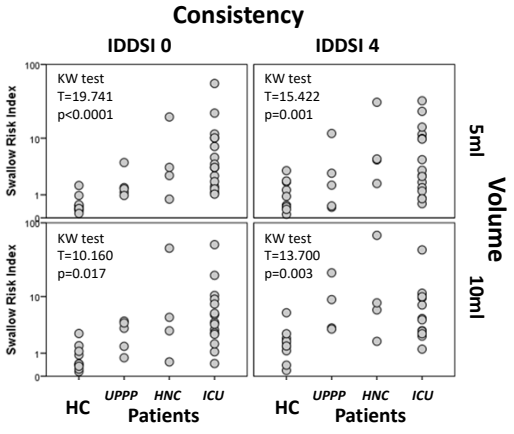
Results: Swallow Risk Index

Pressure-Flow Metrics



Swallow Risk Index (SRI)

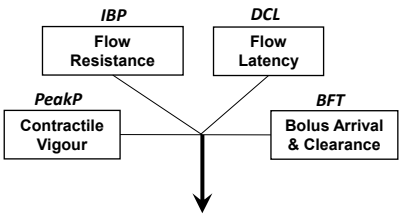
Normal SRI 0-15
Aspiration Risk SRI >15



SRI is higher in dysphagia patients

Results: Swallow Risk Index
(ROC Analysis)

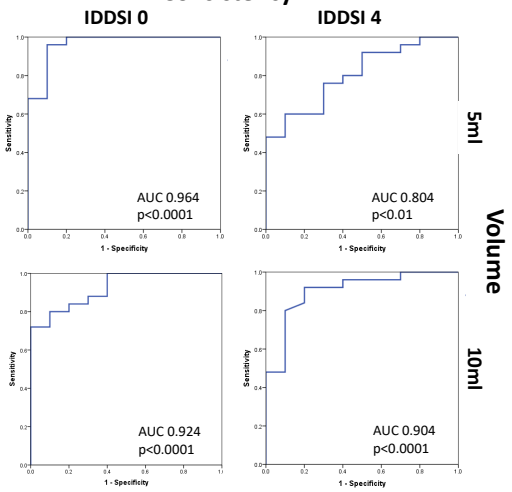
Pressure-Flow Metrics



Swallow Risk Index (SRI)

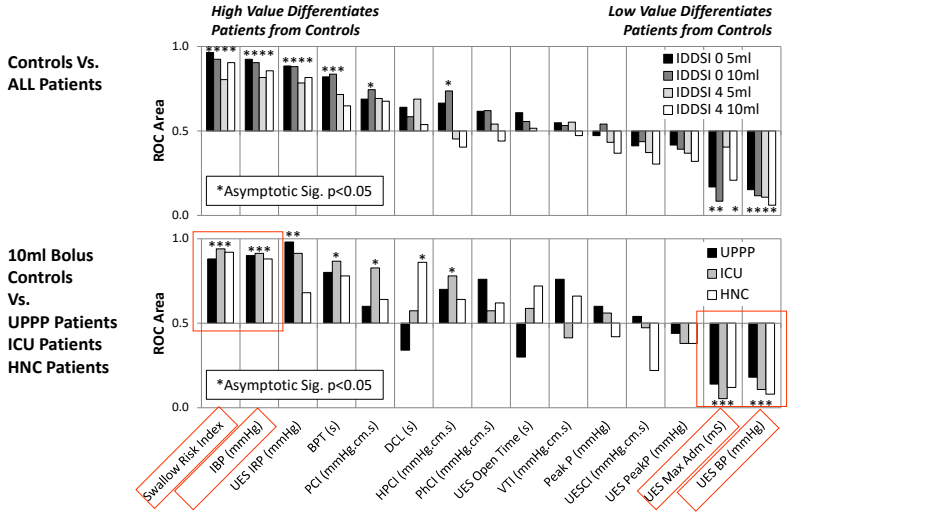
Normal SRI 0-15
Aspiration Risk SRI >15

Consistency



SRI differentiates dysphagia patients

Results: All Measures



SRI and three other measures differentiated patients within all sub-groups;

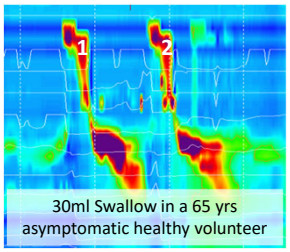
- ***higher*** **intrabolus pressure (IBP)**
- ***lower*** **UES opening admittance (UES Max Adm)**
- ***lower*** **UES basal pressure (UES BP)**

Oral Presentation Dysphagia Research Society
14-18 March 2018 Baltimore,Maryland, USA

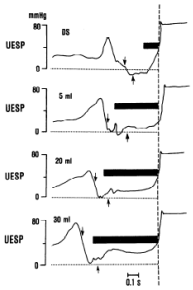
VOLUME EFFECTS ON UPPER (O)ESOPHAGEAL SPHINCTER (UES) OPENING IN AGEING

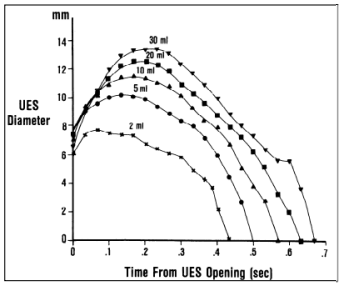
Cock, C[1,2], Doeltgen S[3], Schar M[2], Burgstad C[2], Thompson A[2], Fraser R[1,2] & Omari, T[1,4,5]

[1]Department of Gastroenterology & Hepatology, College of Medicine and Public Health, Flinders University, Adelaide, Australia. [2]Flinders Medical Centre, Adelaide, Australia. [3]Department of Speech Pathology, College of Nursing and Health Sciences, Flinders University, Adelaide, [4]Department of Human Physiology, and [5]Centre for Neuroscience, Flinders University, Adelaide, Australia.



30ml Swallow in a 65 yrs asymptomatic healthy volunteer





Cook et al. 1989 Opening Mechanisms of the Human Upper Esophageal Sphincter

UOS Sensory Swallow Modulation for Volume

UOS opening earlier

UOS opening extent ↑

Contractility ↑(?)

Intrabolus pressure ↑

1. *Cook et al 1989*
2. *Jacob et al 1989*
3. *Cock 2016*

Dysphagia Limit*

Maximum volume that can be swallowed with a single swallow (20ml-30ml)

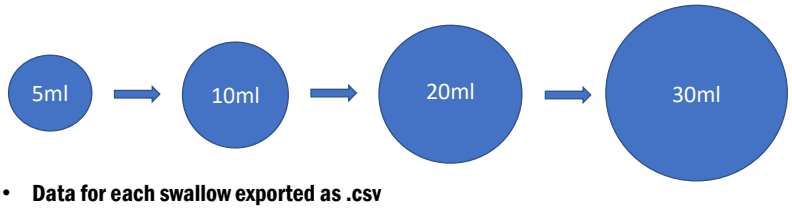
**Ertekin & Aydogdu*

1

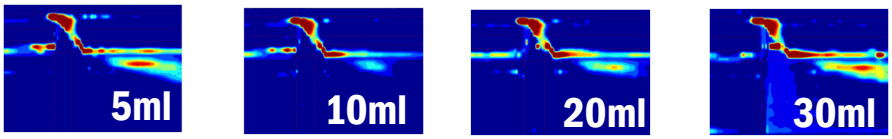
What are the volume effects during P-HRM-I in aging?

What is the dysphagia limit in aging?

- **10 Controls (5M, aged 21-37 yrs) and 15 older (7M, aged 65-94 yrs; 4: 85,90,94,94)**
- **High Resolution Impedance Manometry (36P/16I) MMS Solar/Unisensor**
- **Cued swallowing (requested to "swallow once only"):**

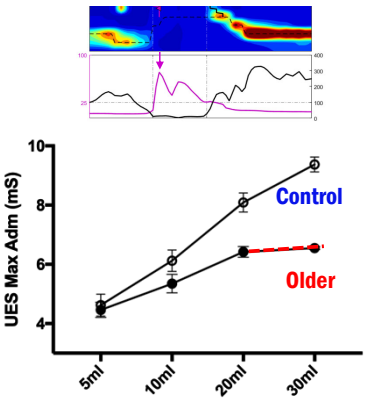


- **Data for each swallow exported as .csv**
- **Analysed via AIMPlot software (*T Omari, Flinders University*)**



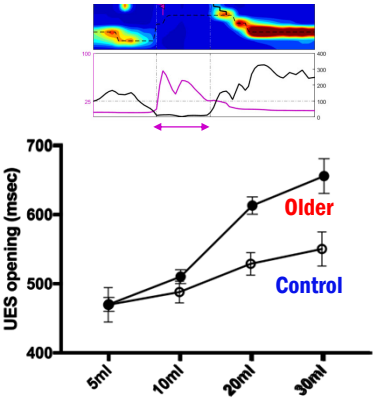
2

UES Opening Extent (UES Max Ad)



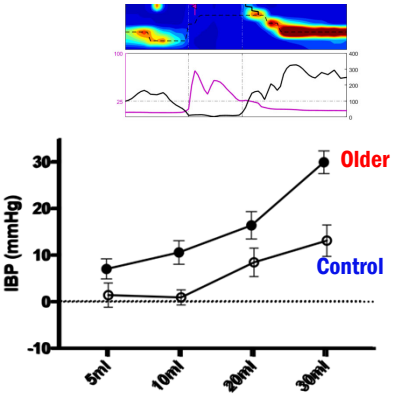
Group
F=13.575;p<0.001
Volume
F=52.896;p<0.001
Gr x Vol
F=8.277;p<0.001

UES Opening Duration (UES RT)



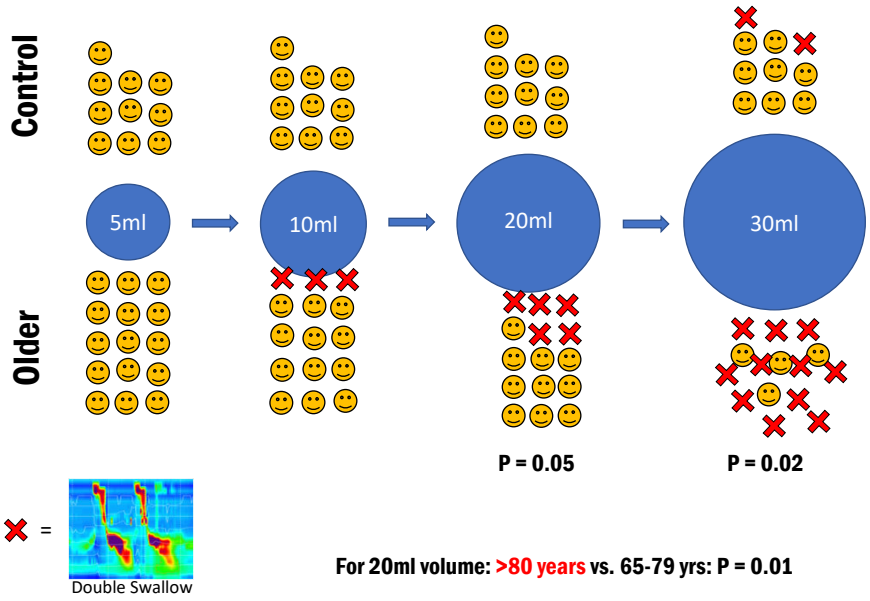
Group
F=3.971;p=0.056
Volume
F=17.179;p<0.001
Gr x Vol
F=3.249;p=0.032

Intrabolus Pressure (IBP)



3

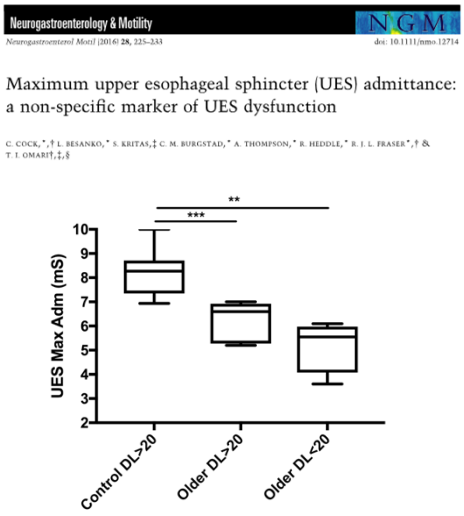
What about the Dysphagia Limit?

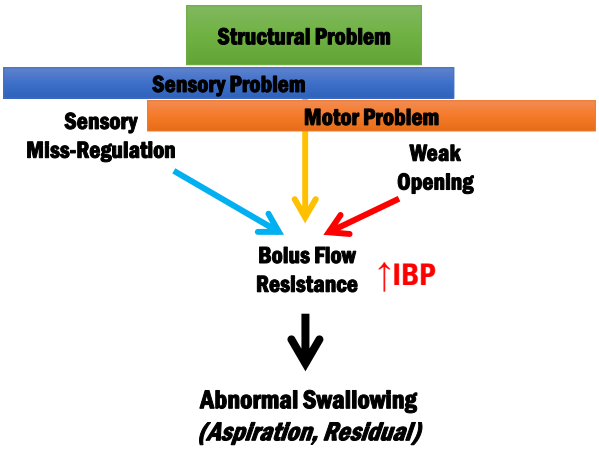


For 20ml volume: >80 years vs. 65-79 yrs: P = 0.01

4

UES Dysfunction





Evidence of "UES Dysfunction" at 20ml in Older

5

Conclusion

- UES opening extent decreased in older &"plateaus" above 20ml
- UES opening duration increased in older (limited data)
- IBP (a measure of "system overload") increased in older
- Dysphagia limit 20 ml for older (but for over 80 years less)
- Evidence of "UES dysfunction" at 20ml in older subjects

6

Failed Esophageal Bolus Clearance Occurs Commonly in Oropharyngeal Dysphagia, Irrespective of Chicago Diagnosis

Charles Cock[1,2], Maartje M Singendonk[3], Julia Greig[4], Allegra Stocks[4], Daphne Mok[4], Mistyka Schar[4,5], Lara Ferris[5], Sebastian Doeltgen[5], Carly M Burgstad[2], Alison Thompson[2], Alexander Barnes[1], Richard Heddle[1,2], Robert JL Fraser[1,2], Nathalie Rommel[6], Taher I Omari[2,7]

Author Affiliations: [1]Department of Gastroenterology & Hepatology, Southern Adelaide Local Health Network, [2]College of Medicine and Public Health, Flinders University, Adelaide, Australia. [3]Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Pediatric Gastroenterology, Amsterdam, The Netherlands. [4]Speech and Language Pathology, Southern Adelaide Local Health Network, Adelaide, Australia. [5]Speech Pathology, College of Nursing and Health Sciences, Flinders University, Adelaide, Australia. [6]Department of Neurosciences, Exp ORL, Deglutology, University of Leuven ("KU Leuven"), Leuven, Belgium. [7]Department of Human Physiology, College of Medicine and Public Health, Flinders University, Adelaide Australia.

Institutions where work was performed: Repatriation General Hospital and Flinders Medical Centre, Adelaide, Australia.

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Abstract

Background & Aims: Dysphagia may have an oropharyngeal (OPD), esophageal cause, or a combined cause; however, there may be an interdependence between OPD and esophageal dysphagia. This study aims to assess esophageal bolus clearance and dysmotility in OPD patients.

Methods: 82 OPD patients (43M, aged 68±13 years, range 36-93 years) and 30 asymptomatic, age-matched controls (13M, 63±14 years, range 33-94 years) were studied. All subjects underwent pharyngeal and esophageal high-resolution impedance manometry of 10x5ml liquid bolus swallows in a tertiary hospital motility laboratory (MMS Solar GI System, Unisensor, 36, 1cm spaced focal pressure sensors; 16, 2cm impedance segments). Swallow data were averaged per subject. Pharyngeal pressure flow analysis was performed using the online software platform swallowgateway.com. Esophageal pressure topography (Chicago Classification v3.0) and impedance-based bolus clearance (50% drop from and return to baseline) were analyzed using MMS diagnostic software. Groups were compared using one-way ANOVA on ranks with post-hoc Dunn's and proportions compared with Fisher's exact test. P-values < 0.05 were considered significant.

Results: Incomplete esophageal bolus clearance occurred in 66/82 (80%) of OPD patients vs. 5/30 (17%) of controls (P < 0.001). Reduced distal esophageal contractility (ineffective esophageal motility and absent contractility) were the most common disorders of peristalsis in the OPD cohort, when compared to healthy controls (45 vs. 17%; P < 0.001). OPD patients also had a high prevalence of peristaltic breaks at the transition zone ("TZ defects"), associated with a tendency for bolus to escape proximally to the distal esophagus (53% of OPD patients with a normal Chicago Classification vs. 7% of controls; P < 0.001)

Conclusions: Incomplete esophageal bolus clearance, increased length of TZ defects and proximal bolus escape occurred in the majority of OPD patients, irrespective of their Chicago Classification diagnosis.

Introduction

Patients who present with dysphagia symptoms may have an underlying oropharyngeal, esophageal, or a combined cause, which can be investigated by endoscopy, radiology and manometry[1-8]. Patient-reported discrimination of symptom location is often unreliable, and dysphagia experienced at the throat level may represent either oropharyngeal dysphagia (OPD) or referred sensation from esophageal dysmotility/obstruction[1-6].

Swallowing in humans consists of four phases: the preparatory, the oral, the pharyngeal, and the esophageal phases[9], all of which can be triggered independently. However, during swallowing, physiological phases are *interdependent* with the contractile response of subsequent phases depending on bolus delivery by the preceding phases[10]. This is particularly relevant to the autonomous smooth muscle distal esophagus. While the oropharynx, upper esophageal sphincter (UES) and proximal esophagus (straited muscle) are under central nervous system control[11,12], the distal esophagus (smooth muscle) is under enteric nervous system control complemented by peripheral reflexes[12-15]. Thus, impaired distal esophageal bolus delivery in OPD may impact distal esophageal contractility.

Recent publications using high-resolution manometry (HRM) have demonstrated examples of abnormal distal esophageal contractility in patients with proven OPD[16,17]. For example, despite vastly different mechanisms of OPD, weak or absent distal esophageal contractile responses occurred in both patients with laryngectomy[16], and in patients with inflammatory myopathies[17]. Equivalent data on proximal esophageal function have not been reported, as the current version of the Chicago Classification for esophageal motor disorders focuses on the distal esophagus only[18]. As the oropharynx and proximal esophagus are neurally integrated, a defective oropharyngeal swallow is likely to exert a greater influence on proximal, rather than distal esophageal contraction.

Measurement of pharyngeal and esophageal swallowing phases using high-resolution impedance manometry (HRIM) has the advantage of simultaneously measuring contractile pressures and bolus transit. This study aims to investigate esophageal bolus transport and contractility in OPD patients to determine the relative contribution of proximal esophageal contractile weakness as a mechanism of failure of esophageal bolus transport, using HRIM.

Methods

OPD Patients

Ninety OPD patients undergoing high-resolution pharyngeal and esophageal manometry were prospectively recruited from a multi-disciplinary speech pathology and gastroenterology swallowing disorders clinic between November 2011 and February 2016. Patients were included if they had objective radiological evidence of OPD based on either Rosenbek penetration/aspiration scale (PAS) score[19] of 5-8 (penetration to the vocal cords or overt aspiration), or significant vallecular/pyriform sinus residue as measured by the normalized residue ratio scale (NRRS score > 0.1)[20,21]. Patients were excluded if they had a history of uncontrolled diabetes mellitus; oropharyngeal, cervical or upper gastrointestinal surgery; had a known allergy to local anesthetic, or were on medications known to affect GI motility. Patients were classified during pharyngeal manometry as having pharyngeal or upper esophageal sphincter (UES) dysfunction or as “other OPD” in case of objective radiological dysfunction accompanied by global swallowing dysfunction or a prolonged bolus dwell time above the UES. They were excluded if they did not fit the descriptions as defined below. Patients also completed the EAT10 questionnaire[22].

Controls

OPD patients were compared to a cohort of age-matched healthy volunteer subjects who were recruited via community advertisement (controls). Subjects reported no symptoms of dysphagia, did not have a history of diabetes; oropharyngeal, cervical or upper gastrointestinal

surgery; allergy to local anesthetic and were not taking any medications known to alter gut motility.

Informed Consent

All controls and OPD patients signed written, informed consent before undertaking any study related procedures (OFN No. 283.11 & 444.14; Southern Adelaide Clinical Human Ethics Research Committee).

Instrumental Assessments (Radiology and Endoscopy)

Study subjects were assessed by videofluoroscopic swallowing studies undertaken in the radiology suite at Repatriation General Hospital, Adelaide, Australia using Siemens (Siemens, Munich, Germany) video fluoroscopy equipment. Frame rates of 15 frames per second (fps) were used to assess oropharyngeal pulmonary aspiration[23], while lesser frame rates (7.5 fps) were at times used to assess bolus transit. Several boluses were assessed, determined by clinical need, but including 5ml international dysphagia diet standardization initiative (IDDSI)[24] consistency = 0, radio-opaque boluses used for comparison in this study. In order to exclude eosinophilic esophagitis or strictures, upper gastrointestinal (GI) endoscopies were undertaken at the Repatriation General Hospital (Pentax, Tokyo, Japan) or Flinders Medical Centre (Olympus, Tokyo, Japan) in the majority of patients. A small proportion of patients in this cohort had upper GI endoscopies performed in private medical facilities.

High Resolution Manometry

Subjects were studied in the motility laboratories or radiology suites at Flinders Medical Centre and Repatriation General Hospital, Adelaide, Australia. A Medical Measurement Systems (MMS) Solar GI system (MMS, Enschede, Netherlands) with a Unisensor 3.2mm diameter recording catheter (Unisensor, Wiesendangen, Switzerland) was used. The manometry assembly had 32, 1cm-spaced, focal pressure sensors, and 16, 2cm length, impedance segments. Subjects were intubated via an anaesthetized nostril (2% Lignocaine). The manometry catheter array was insufficient to straddle the entire region from above the

velopharynx to the stomach in most subjects and was therefore was positioned initially over the distal esophagus (with minimum 2-3 pressure sensors in the stomach) and bolus swallows were captured in a right lateral recumbent position. Distal esophageal recordings obtained in this manner were used to assess esophageal bolus clearance. The catheter was then re-positioned across the pharynx (from the velopharynx to esophageal transition zone) and further swallows were captured in the upright head neutral position. Averaged data from a minimum of 5 x 5ml thin liquid boluses (IDDSI level = 0)[24] are reported[25].

Diagnosis of Pharyngeal Motor Disorders

Pharyngeal pressure impedance recordings were exported (single ASCII file) and analyzed via an online software application (swallowgateway.com)[25] (Figure 1).

Despite an increasing number of clinical studies using high-resolution pharyngeal manometry (HRPM), there is currently no consensus-based classification system for diagnosis of pharyngeal disorders[26]. Therefore, normative data from the controls (supplementary Table A) were used to classify UES dysfunction (evidence of UES restriction), pharyngeal dysfunction (evidence of reduced contractility), or "other" dysfunction as defined below.

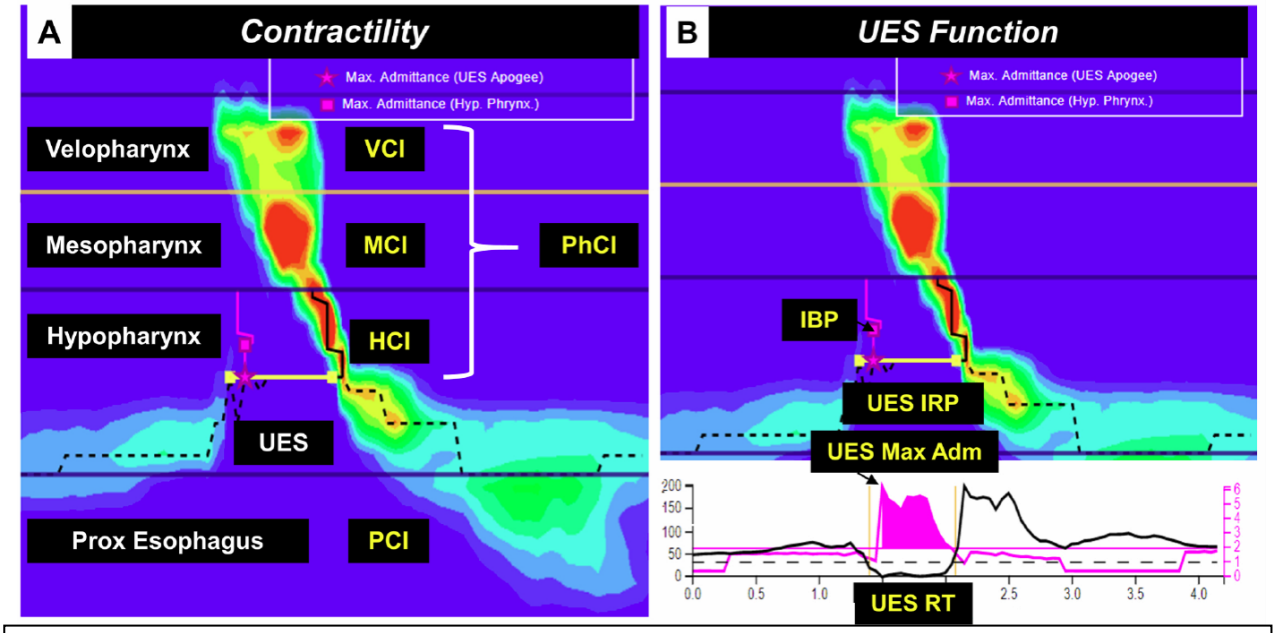

Figure 1. Analysis of the pharyngeal pressure-impedance topography to define contractility (1A), and upper esophageal sphincter (UES) relaxation and opening (1B), Contractile integrals are calculated for the velo-, meso-, and hypopharynx; collectively the pharyngeal contractile integral (PhCI) and proximal esophagus (PCI) (1A). Bolus flow through the UES (purple) is determined by analyzing the impedance signal (which has been inverted and shaded to show bolus presence). Intrabolus pressure (IBP) a predictor of UES restriction[32] is measured at 1cm above the sphincter apogee position. UES relaxation extent (as integrated relaxation pressure – UES-IRP) and time (UES-RT) are also measured. UES maximum admittance (UES Max Adm) is a metric indicating extent of maximum UES opening.

UES dysfunction was defined by hypopharyngeal intrabolus pressure[27], and/or the UES 0.25 second integrated pressure[26-28] above 95th percentile values of controls (Figure 1B; Supplementary Table A). UES intrabolus pressure and IRP are correlates of UES restriction[27.]

Pharyngeal weakness was defined by a universal (composite pharyngeal contractile integral/PhCI) or regional contractile integral (regional mean pressure above atmospheric x length x duration)[28] for velo-, meso- and hypopharynx regions below the 5th percentile of controls (Figure 1A; Supplementary Table A).

OPD patients who did not fit the schema for UES or pharyngeal dysfunction but who nevertheless had other biomechanical evidence of abnormal swallowing, including elevated global swallow risk index[29,30], reduced UES maximum admittance[31], and/or a prolonged bolus presence time (BPT)[26], were categorized as "other" dysfunction. Eight cases (10%) did not have any manometrically identifiable oropharyngeal manometric dysfunction, despite radiological abnormalities. These cases were excluded from further analyses or descriptions.

Diagnosis of Esophageal Motor Disorders

Chicago Classification of esophageal pressure topography version 3.0 was applied[18]. Major disorders of esophageal peristalsis included all subtypes of achalasia, esophagogastric junction outflow obstruction (EGJOO), absent contractility, distal esophageal spasm, and hypercontractile ("jackhammer") esophagus. Minor disorders of peristalsis included ineffective esophageal motility (IEM) and fragmented peristalsis. Normal motility was diagnosed in subjects who did not meet either major or minor criteria.

Esophageal Bolus Clearance

The effectiveness of esophageal bolus clearance for each esophageal swallow was assessed by intraluminal impedance, using a decrease of 50% from baseline. This was used to define bolus entry and sustained (≥ 5 seconds) increase of 50% to the original baseline, to define bolus clearance at the impedance segment level[32-34] (Figure 2). Peristaltic breaks, including transition zone defects, were defined as axial breaks in the 20mmHg isobar. *Complete* bolus

clearance was defined as bolus entry, followed by clearance at *all* subsequent impedance sites along the entire esophagus (proximal and distal) for at least 80% of swallows[33,34] (Figure 2A). Bolus clearance was defined as *incomplete* when there was bolus entry without clearance for one or more impedance segments[34] (Figure 2B). As a consequence, bolus escape due to increased length of peristaltic breaks in the transition zone ("TZ defects")[35] (Figure 2C-E) were also classed as incomplete bolus clearance.

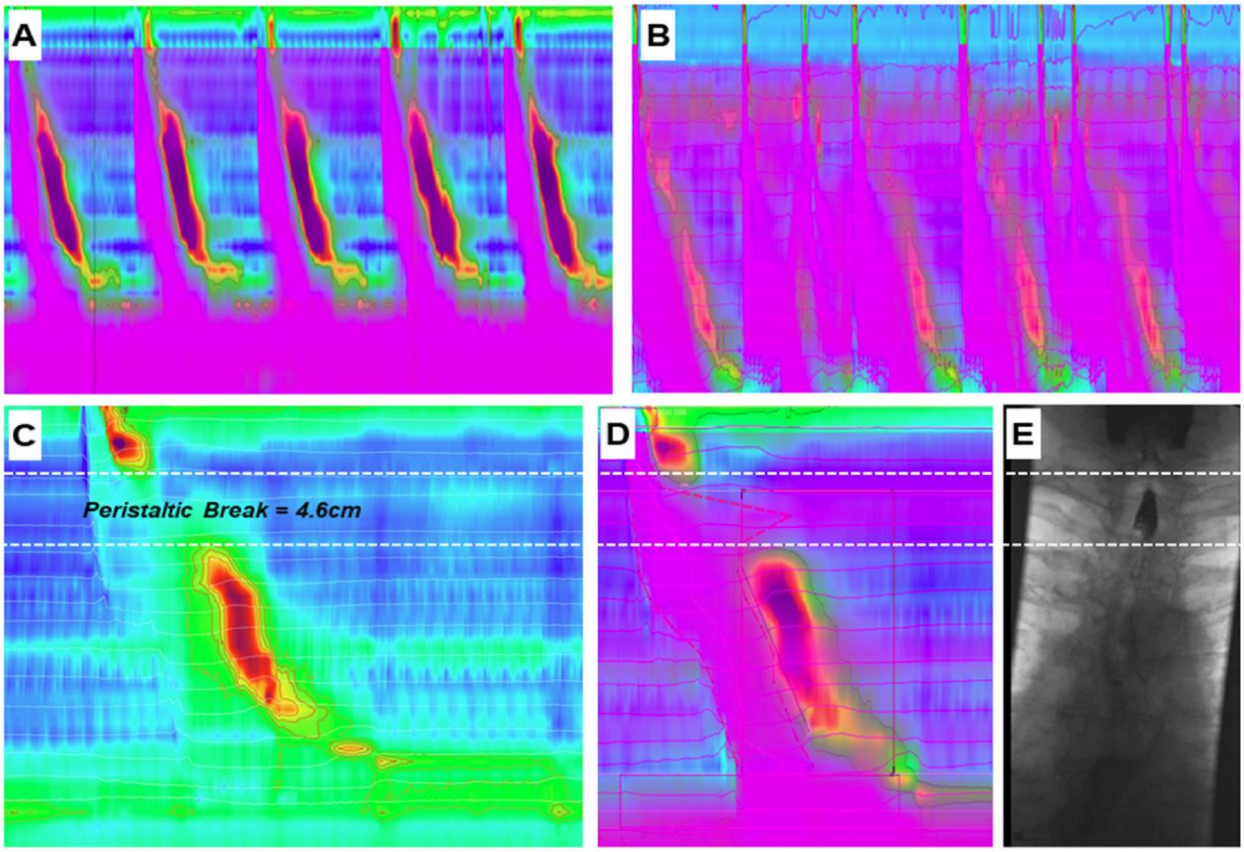

Figure 2. Figure shows example of esophageal pressure topography, impedance-based bolus clearance (purple) and radiology. Examples of complete bolus clearance in a control subject (2A), incomplete clearance in an oropharyngeal dysphagia patient (2B) and proximal bolus escape occurring in the space between the broken lines (incomplete clearance) in association with increased peristaltic break length between proximal and distal 20mmHg isocontours (2C) with persistent signal in the proximal esophagus (2D) and evidence of proximal esophageal bolus retention on AP radiology (2E), in a 49 year-old female with oropharyngeal dysphagia due to inclusion body myositis.

Statistical analysis

Data were assessed for normality before undertaking statistical analyses. The majority of data in this study were non-normally distributed and thus non-parametric statistical analyses were undertaken using Sigmaplot 14.0 (Systat software, San Jose, Ca., USA).

One-way ANOVA on ranks (Kruskal-Wallis) with post-hoc pairwise Dunn's test was undertaken. Proportions were compared using Fisher's Exact Test. A P-value of <0.05 was considered significant.

Results

Study Subjects

Distribution of OPD patients based on the results of pharyngeal manometry are displayed as Figure 3.

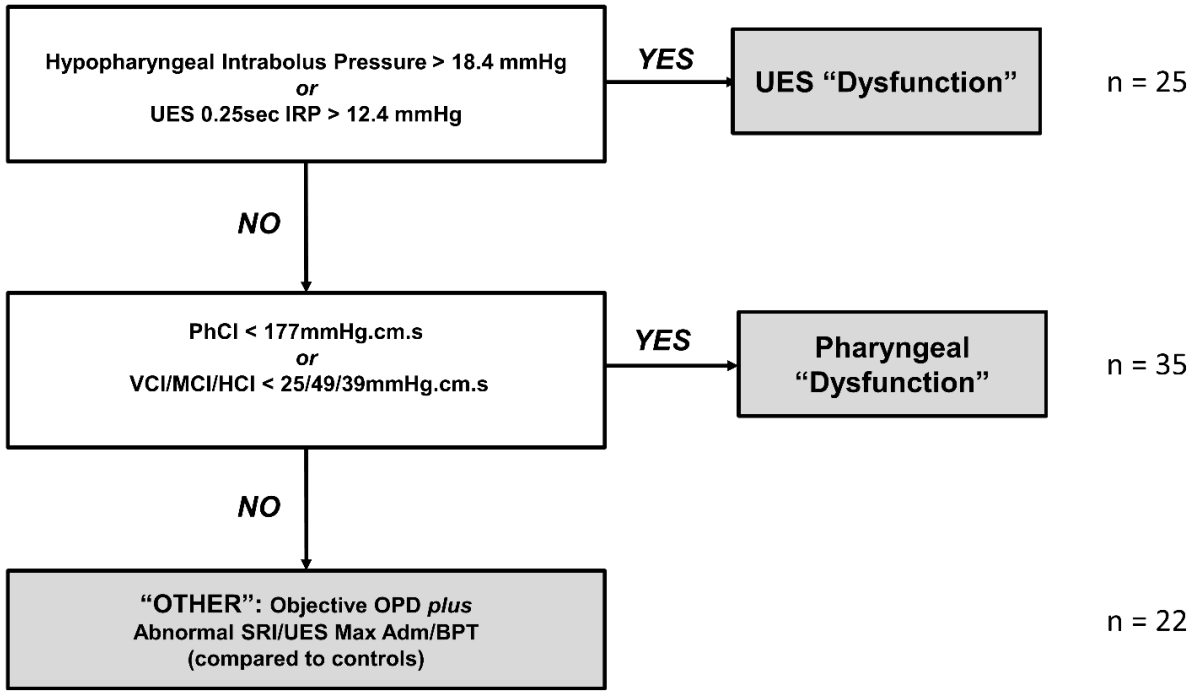

Figure 3. Classification of OPD patients as Pharyngeal Dysfunction, UES Dysfunction or "Other OPD" based on normative data from healthy volunteers (controls).

Table 1 contains subject demographics, radiology data and impedance-based esophageal bolus clearance; and the distribution of various pathologies (reasons for referral) for OPD patients.

Table 1 Study Subjects	**Controls**	**OPD Patients**		
		UES Dysfunction	**Pharyngeal Dysfunction**	**Other OPD**
Number (n)	30	25	35	22
Age in years (mean + SD)	63±14	68±13	66±12	69±15
(range)	39-94	40-91	36-85	33-93
Male Gender n (%)	15 (50)	15 (60)	16 (46)	12 (55)
EAT10 Score (range)[22]	0 (0-3)	19 (4-38)	22 (4-40)	28 (17-40)
Radiology				
Penetration/Aspiration (PAS)[19]	1[1;2]	7[2;8]*	2[1;7]	2[1;5]
Vallecular Residue (NRRSv)[20]	0[0;0.02]	0.24[0.15;0.98]**	0.41[0.18;1.02]***	0.28[0.12;1.16]**
Pyriform Residue (NRRSp)[20]	0[0;0]	0.04[0;0.19]	0.55[0.11;1,21]**	0.05[0;0.69]
Esophageal Bolus Clearance				
Complete n (%)	25 (83)	5 (20)***	6 (17)***	5 (23)***
Incomplete n (%)	5 (17)	20 (80)***	29 (83)***	17(77)***
Chicago Classification (v3.0)				
Major (Absent/EGJOO/DES)	0 (0/0/0)	4 (2/1/1)*	11 (7/3/1)***	4 (2/1/1)*
Minor (IEM/Fragmented)	5 (5/0)	7 (6/1)	10 (7/3)	8 (5/3)
Normal	25	14*	14***	10**
Reasons for Referral				
CNS Pathology		5	6	5
Neurodegenerative		10	7	4
Neuromuscular		1	11##	0
Structural Pathology		6	8	11
Unknown Cause of OPD		3	3	2

* P < 0.05; ** P < 0.01, ***P < 0.001 vs. controls; ## P < 0.01 vs. Other groups of OPD patients
EGJOO – Esophagogastric junction outflow obstruction; DES – Distal esophageal spasm; IEM – Ineffective esophageal motility

Chicago Classification, Esophageal Pressure Topography and Bolus Clearance

OPD patients had a greater incidence of disordered esophageal body motility compared to controls. Whilst thirty-eight OPD patients (46%) were characterized with normal motility, twenty-six OPD patients had a minor disorder (32%) and eighteen a major disorder (22%) of peristalsis (Figure 4). Twenty-five controls were characterized with normal motility (83%), the remainder had a minor disorder, namely ineffective esophageal motility (17%). Reduced distal esophageal contractility (ineffective esophageal motility and absent contractility) were the most common disorders of peristalsis in the OPD cohort, when compared to healthy controls (45 vs. 17%; $P < 0.001$). TZ defects of 2-5cm in length occurred commonly in OPD patients, even those with “normal” motility. Fragmented peristalsis defined as TZ or other peristaltic defects greater than 5cm in length occurred exclusively in OPD patients (9%).

Observed peristaltic abnormalities were associated with incomplete esophageal bolus clearance in OPD patients (Figure 4). Unlike controls who always demonstrated complete bolus clearance when peristalsis was normal (Chicago Classification v3.0), two thirds of OPD patients with normal oesophageal motility demonstrated failed bolus clearance. Of those, a preponderance of TZ defects 2-5 cm in length occurred in 80% of OPD patients with normal peristalsis (Figure 3). Furthermore, 53% of OPD subjects showed proximal bolus escape, consistent with retention at the TZ, compared to 7% of controls ($P<0.001$). Thus, incomplete bolus clearance is a dominant feature of OPD; the extent of which was, to a degree, masked by the application of the Chicago Classification (v3.0). The Chicago Classification criteria primarily focuses on the diagnosis of disorders of the distal esophagus and lower esophageal sphincter, whilst abnormal esophageal findings in OPD mostly occurred proximally.

Additional Results

Normative values for pharyngeal manometry in controls are included in online supplementary Table A. Results for high-resolution pharyngeal manometry (HRPM) in OPD patients with UES

dysfunction, pharyngeal dysfunction, and “other” classifications are congruent with their descriptors and are included in online supplementary Table B.

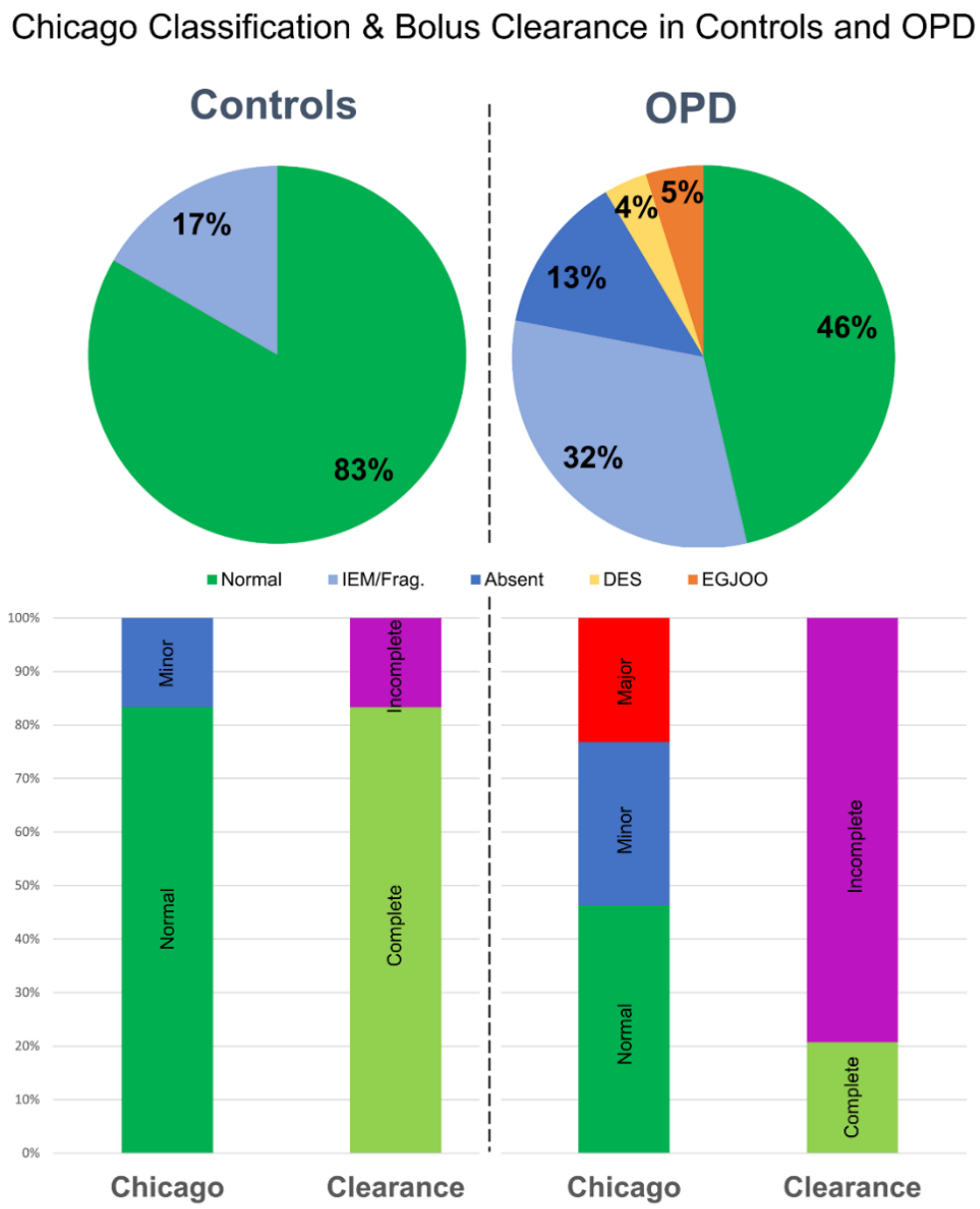

Figure 4. Chicago categorization and bolus clearance in 30 controls and 82 OPD patients. Bolus clearance is incomplete in 80% of OPD and 17% of controls (P = 0.001). Controls have a normal esophageal pressure topography (green) with complete clearance (light green), or minor disorders of peristalsis (blue), and incomplete clearance (purple). OPD patients often have incomplete clearance (purple) despite normal peristalsis (green) and invariably incomplete clearance (purple) for both minor (blue) and major (red) disorders of peristalsis.

Discussion

This study examined the mechanisms of esophageal bolus transport in patients with established OPD. The main findings were; i) that OPD patients as a whole demonstrated Chicago Classification disorders indicative of reduced distal esophageal contractility (IEM, fragmented, absent), ii) failed bolus transport was associated with reduced contractility in the proximal esophagus and transition zone (TZ), and iii) these features did not differ in relation to either etiology of primary OPD, or the biomechanically characterized nature of pharyngeal dysfunction.

At this time, the Chicago Classification system only focuses on the distal esophagus and LES, while abnormal esophageal findings in OPD patients mostly occurred proximally. Past studies of esophageal manometry in OPD demonstrated a preponderance of minor distal esophageal motility disorders[16,17,36,37]. Data from the current study demonstrated both minor and major disorders indicative of reduced distal esophageal contractility and adds further information in relation to esophageal bolus transport, which was incomplete for the majority (80%) of OPD patients. This included two thirds with normal distal motility by the Chicago Classification. In the majority of cases of incomplete transit, proximal bolus escape occurred associated with TZ defects. Similarly, bolus escape at the level of the aortic arch, especially of increased consistency boluses, also occurred commonly on radiology studies in OPD patients, while distal esophageal motility remained intact. Bolus escape in the proximal region, rich in sensory innervation[38], may explain patient difficulty in localizing the site of their dysphagia, and possible clinician misinterpretation of site and cause of dysphagia, given the proposed interdependence of contractile responses of the pharyngeal and esophageal phases of the dysphagia. Reduced bolus-based stimulation of distal contractile mechanisms or other biomechanical effects related to the speed and extent of bolus entry in the distal esophagus may further explain findings in the current study.

Proximal peristalsis is controlled by the central nervous system[11,12] and therefore oropharyngeal neural pathology may explain attenuated activation of proximal contractility. The mechanism of reduced distal contraction in some patients with OPD is less clear, as smooth muscle contraction in the distal esophagus is under separate control by the enteric nervous system[13]. However, the activation of intramural circuits by bolus distention, which precedes contraction, is an important determinant of contractile vigor[10-12,39,40]. Thus, impaired propulsion and/or restricted flow at sites upstream may reduce esophageal bolus distention downstream, in turn attenuating the smooth muscle contractile response. If correct, secondary peristalsis should be preserved in OPD; which requires further investigation.

This study has some limitations which are important to acknowledge. Whilst a diverse group of OPD patients are included, this dataset is by no means exhaustive and therefore insufficient to determine whether these findings apply to all OPD diagnoses, or only particular subgroups. It has to be acknowledged that the simple classification applied here would fail to identify patients with multiple superimposed biomechanical dysfunctions, such as UES restriction in the context of pharyngeal propulsive failure. Our classification, while helpful to stratify the study group, is not proposed as a definitive classification for OPD and 10% of subjects did not fit the classification, despite objective evidence of oropharyngeal dysfunction in the form of oropharyngeal residue. This remains an important topic for future consensus-based discussions amongst experts in the field. Results were obtained on liquid bolus trials, and possible impact of oesophageal clearance of textured consistencies could be considered for future studies, of note some subjects complain of dysphagia only to increased consistency boluses and recent work have focused on distal esophageal motility disorders related to solid boluses[41].

This study provides novel insights into the association of OPD with impaired esophageal bolus transit and disorders of reduced distal esophageal peristalsis. Proximal failure of bolus transit occurred frequently, associated with an increased length of TZ peristaltic defects and

irrespective of Chicago Classification based diagnosis. The relevant mechanisms may include damage to CNS innervation governing proximal peristalsis or reduced activation of intramural mechanisms regulating distal peristalsis.

Table 2 Pharyngeal and Esophageal Metrics related to Esophageal Clearance in Controls and OPD Patients and in OPD with Pharyngeal or UES Dysfunction (Median values with 25th and 75th percentiles in square brackets shown).

	Controls	**OPD Patients**	
	Complete Clearance (n=25)	**Complete Clearance (n=17)**	**Incomplete Clearance (n=65)**
Swallow Risk Index	2[1;3]	**6[3;18]****	**4[2;11]***
UES Max Adm (mS)	6.5[5.8;7.4]	**3.9[3.3;4.2]*****	**3.8[3.5;4.4]*****
PhCI (mmHg.cm.s)	369[254;592]	377[196;490]	332[220;489]
VCI(mmHg.cm.s)	65[44;93]	66[38;142]	58[31;94]
MCI (mmHg.cm.s)	134[84;218]	138[68;210]	143[71;206]
HCI (mmHg.cm.s)	122[78;183]	83[56;147]	101[68;158]
IBP (mmHg)	6.1[0.6;10.7]	8[4.1;27.4]	8.4[2.5;16.5]
UES IRP (mmHg)	-1.5[-4.2;3.1]	5.1[-0.6;16.9]	1.5[-4;6.6]
UES RT (msec)	649±17	638±22	663±12
PCI (mmHg.cm.s)	305[127;463]	298[206;399]	233[153;373]
Peristaltic Breaks (cm)	0.2[0;1.6]	0.9[0;1.7]	**3.4[2.1;5.5]*****
DCI (mmHg.cm.s)	1853[921;2179]	1803[1043;6043]	1140[374;2681]
IRP4 (mmHg)	11[8;17]	8[5;16]	10[5;21]
DL (sec)	6.5[5.9;7.4]	6.5[5.3;7.2]	6.6[5.7;7.7]

Supplementary Tables

Table A: Normative values (based on 30 controls aged 39-94 years; mean age 63±14 years)

	Average ±SEM	Median [25P;75P]	5th Percentile	95th Percentile
Global Dysfunction				
Swallow Risk Index	1.9±0.3	2[1;3]	0.2	**4.5**
UES Max Adm (mS)	6.3±0.3	6.2[5.2;6.8]	**4.4**	9.0
Pharyngeal Contractility				
PhCI (mmHg.cm.s)	421±37	365[259;581]	**177**	751
VCI(mmHg.cm.s)	84±18	63[45;86]	**25**	146
MCI (mmHg.cm.s)	150±16	133[95;208]	**49**	307
HCI (mmHg.cm.s)	143±16	124[81;173]	**39**	287
UES Function				
IBP (mmHg)	5.7±1.3	6.0[0.9;9.3]	-7.3	**18.4**
UES IRP (mmHg)	0.1±1.1	-1.3[-3.8;2.8]	-7.0	**12.4**
UES RT (msec)	638±15	623[577;717]	**506**	764
Proximal Esophagus				
PCI (mmHg.cm.s)	311±40	286[138;437]	**62**	740
Transition Zone				
Peristaltic Breaks	1.4±0.4	0.4[0;2.1]	0	**5.7**
Distal Esophagus				
DCI (mmHg.cm.s)	1782±263	1578[838;2097]	**254**	4738
IRP4 (mmHg)	11±1	11[8;15]	3	**20**
DL (sec)	6.9±0.3	6.5[6;7.5]	**5.4**	9.5

Table B: High-Resolution Impedance Manometry in Controls and Subgroups of OPD

	Controls	**OPD Patients**		
	Complete Clearance (n=25)	**Pharyngeal Dysfunction (n=35)**	**UES Dysfunction (n=25)**	**Other (n=22)**
Global Dysfunction				
Swallow Risk Index	2[1;3]	3[1;8]	**12[5;23]*****	3[2;5]
UES Max Adm (mS)	6.5[5.8;7.4]	**3.9[3.6;4.5]*****	**3.9[3.3;4.4]** ***	**3.9[3.5;4.3]** ***
Pharyngeal Contractility				
PhCI (mmHg.cm.s)	369[254;592]	**199[125;341]*****	460[[306;597]	420[328;498]
VCI(mmHg.cm.s)	65[44;93]	**31[8;46]*****	83[65;149]	91[70;146]
MCI (mmHg.cm.s)	134[84;218]	**62[38;149]***	202[126;262]	177[133;229]
HCI (mmHg.cm.s)	122[78;183]	**72[38;104]***	120[83;182]	107[88;151]
UES Function				
IBP (mmHg)	6.1[0.6;10.7]	3.4[-0.4;7.2]	**26.7[19.1;34.1]*****	5.9[3.9;9.5]
UES IRP (mmHg)	-1.5[-4.2;3.1]	0.1[-2.5;3.7]	**10.4[-2.4;19.6]****	0.4[-2.0;4.6]
UES RT (msec)	649±17	659±17	640±17	681±19
Proximal Esophagus				
PCI (mmHg.cm.s)	305[127;463]	211[140;325]	337[204;498]	240[199;303]
Transition Zone (TZ)				
TZ Defect (cm)	0.2[0;1.6]	**2.9[1.6;5.6]*****	**2.1[0.8;4.6]***	**2.6[1;3.8]*****
Distal Esophagus				
DCI (mmHg.cm.s)	1853[921;2179]	1174[279;2823]	1862[1011;3928]	1064[478;3181]
IRP4 (mmHg)	11[8;17]	6[4;16]	18[6;24]	10[6;13]
DL (sec)	6.5[5.9;7.4]	6.5[5.5;7.4]	6.4[5.7;7.1]	7.0[5.9;7.7]

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Appendix D: Presentations and Publications

Appendix D: List of Publications and Presentations related to Thesis

Abstracts & Oral Presentations

1. Cock C, Mok D, Kritas S, Burgstad C, Thompson A, Besanko L, Heddle R, Greig J, Ferris L, Fraser R, Omari T. Pharyngeal Automated Impedance Manometry Pressure Flow Analysis Predicts Degree of Post Swallow Residue During Non-concurrent Modified Barium Swallow Studies. J Neurogastroenterol Motil 2014; 20(4)(Suppl. 2): S7. Oral Presentation FNM 2014 Guangzhou, China

2. Cock C, Kritas S, Burgstad C, Thompson A, Besanko L, Heddle R, Fraser R, Omari T. High-resolution Manometric Correlates of Esophageal Bolus Clearance in Aging Using Chicago Classification Criteria. J Neurogastroenterol Motil 2014; 20(4)(Suppl. 2): S122

3. Cock C, Kritas S, Burgstad C, Thompson A, Besanko L, Heddle R, Fraser R, Omari T. High-resolution Manometric Correlates of Esophageal Bolus Clearance in Aging Using Automated Impedance Manometry Pressure Flow Analysis. J Neurogastroenterol Motil 2014; 20(4)(Suppl. 2): S122

4. Cock C, Kritas S, Besanko L, Burgstad CM, Thompson A, Heddle R, Fraser RJ, Omari TI. Integrated relaxation pressure (IRP4) increases during viscous swallowing in aged subjects. ANGMA conference proceedings 2015 (Poster 8)

5. Cock C, Kritas S, Burgstad CM, Thompson A, Besanko L, Heddle R, Fraser RJ, Omari TI. Upper esophageal sphincter (UES) maximum admittance identifies dysphagia due to neuromuscular and structural pathology. ANGMA conference proceedings 2015 (Poster 9)

6. Myers J, Cock C. Pharyngo-oesophageal physiology in vivo. ANGMA conference proceedings 2015 Oral Presentation ANGMA Conference, Adelaide, Australia

7. Mok D, Cock C, Ferris L, Scheerens C, Rommel N, Omari T. Vallecular and Piriform Residue during Modified Barium Swallow Studies in Patients and Controls. Speech Pathology Australia Conference Proceedings 2015 Oral Presentation, Canberra, Australia

8. Cock C, Mok D, Ferris L, Scheerens C, Rommel N, Omari T. Reliability of the Normalized Residue Ratio Scale (NRRS) during Modified Barium Swallow (MBS) studies in Patients and Controls. Speech Pathology Australia Conference Proceedings 2015 Oral Presentation, Speech Pathology, Canberra, Australia

9. Cock C, Jones CA, Hammer M, Omari TI, McCulloch TM. Upper esophageal sphincter opening is modulated by bolus volume. Dysphagia Research Society, Tucson, Arizona (Poster – March 2016)

10. Cock C, Besanko LK, Burgstad CM, Heddle R, Fraser RJ, Omari TI. Age-Related Impairment of EGJ-Relaxation and Bolus Flow Time. Gastroenterol 2016; 150(4): S288. Poster Digestive Diseases Week (DDW), San Diego, Ca, USA

11. Cock C, Leibbrandt RE, Costa M, Dinning PG, Omari TI. Oesophageal neuromechanical states and bolus perception in healthy volunteers. J Gastroenterol Hepatol 2016; 31(Suppl. 2):169 Oral presentation, Australian Gastroenterology Week (AGW), Adelaide, Australia

12. Kokkinn K, Singendonk MMJ, Schar M, Omari TI, Cock C. Reliability of oesophageal pressure topography metrics. J Gastroenterol Hepatol 2016; 31(Suppl. 2):172 (Poster)

13. Rigney L, Cock C, Doeltgen SH. The effects of transcranial direct current stimulation (tDCS) on corticobulbar excitability and swallowing. Dysphagia Research Society March 2017, Portland, Or, USA

14. Cock C. The Biomechanics of Swallowing Dysfunction in Motor Neurone Disease. MND SA Research Symposium. Oral presentation MND Research Forum, Adelaide, Australia

15. Cock C. Novel analysis approaches for assessing oesophageal function in health and disease. Australasian Neurogastroenterology and Motility Association (ANGMA) conference proceedings. Oral presentation ANGMA, Melbourne, Australia

16. Cock C, Schar M, Burgstad C, Thompson A, Heddle R, Fraser RJL, Omari TI. Normative Chicago Classification and Pressure Flow Metrics for Solid Bolus Swallows in the Upright Posture during High-resolution Impedance Manometry. Australasian Neurogastroenterology and Motility Association (ANGMA) conference proceedings (Poster)

17. Cock C, Doeltgen S, Savilampi J, Omari TI. How opioids effect oesophageal motility and flow. Australasian Neurogastroenterology and Motility Association (ANGMA) conference proceedings (Poster)

18. Cock C, Thompson A, Burgstad C, Heddle R. Clinical utility of upright viscous and solid bolus swallows during high-resolution impedance manometry. J Gastroenterol Hepatol 2017; 32(Suppl 2): 172-178 AGW (Poster)

19. Cock C, Doeltgen S, Schar M, Burgstad C, Thompson A, Fraser R, Omari T. Effortful swallowing maneuver restricts UES opening in healthy older volunteers. September 2017. Oral Presentation - European Society for Swallowing Disorders, Barcelona, Spain.

20. Cock C, Doeltgen S, Schar M, Burgstad C, Thompson A, Fraser R, Omari T. Volume effects on upper esophageal sphincter opening in ageing. Oral

Presentation - European Society for Swallowing Disorders, Barcelona, Spain & Dysphagia Research Society, March 2018, Baltimore, Maryland, USA

21. Cock C. High Resolution Pharyngeal Manometry with Impedance. Oral Presentation Dysphagia Research Society, March 2018, Baltimore, Maryland, USA

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**Joint First Author*

Appendix E: Study Questionnaires

Brief Esophageal Dysphagia Questionnaire*

Sydney Swallow Questionnaire*

Laboratory Questionnaires

*Redacted for copyright reasons

Date: _____

Affix label here

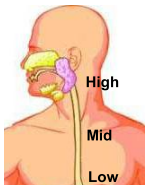
Viscous Swallows - *5ml thickened apple juice*

Please rate if you feel any sensation of material being stuck on scale below and indicate its location on the diagram

0 = Material is <u>not</u> stuck and I feel <u>no</u> sensation *10 = Material is **stuck** and I feel **pain***

Swallow 1

0 1 2 3 4 5 6 7 8 9 10



Swallow 2

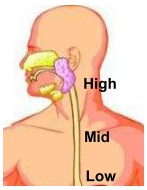
0 1 2 3 4 5 6 7 8 9 10

Swallow 3

0 1 2 3 4 5 6 7 8 9 10

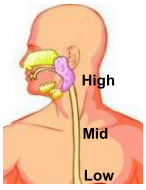
Swallow 4

0 1 2 3 4 5 6 7 8 9 10



Swallow 5

0 1 2 3 4 5 6 7 8 9 10



Date: _____

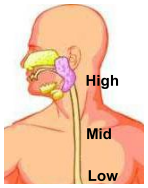
Affix label here

Solid Swallows – *1/8 white bread*

0 = Material is <u>not</u> stuck and I feel <u>no</u> sensation *10 = Material is **stuck** and I feel **pain***

Swallow 1

0 1 2 3 4 5 6 7 8 9 10



Swallow 2

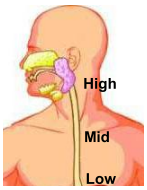
0 1 2 3 4 5 6 7 8 9 10

Swallow 3

0 1 2 3 4 5 6 7 8 9 10

Swallow 4

0 1 2 3 4 5 6 7 8 9 10



Swallow 5

0 1 2 3 4 5 6 7 8 9 10