(Illustrations by J Myers)

Risk and Pathogenesis of Dysphagia Related to Antireflux Surgery

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THESIS ABSTRACT

Dysphagia, the difficulty of swallowing food or drink, is experienced by some patients with gastro-oesophageal reflux disease and is a common adverse effect of antireflux surgery, a procedure involving diaphragmatic hiatal repair and fundoplication. Dysphagia after surgery in the absence of recognisable anatomical abnormalities is poorly understood and thus difficult to treat.   Despite modifications to surgical techniques, post-operative dysphagia remains unpredictable (Chapter 1). My aim is to identify patients at risk and the causes of dysphagia related to antireflux surgery.

A fundamental premise of this thesis is that objective measurements hold the key to understanding post-fundoplication dysphagia. Five prospective studies are presented which evaluate oesophageal body or oesophago-gastric junction (OGJ) function with regards to: early new-onset and late persistent post-operative dysphagia. Objective data were gathered using: i) luminal manometry alone; ii) impedance combined with manometry, to assess relationships between oesophageal pressure and bolus flow; and iii) three-dimensional pressure recordings of expiratory and inspiratory radial OGJ pressure to assess the contribution of hiatal repair and fundoplication to post-operative dysphagia.

These studies show: an 'oesophageal ileus' in the early post-operative period, with global failure of primary peristalsis in 70% of patients after total fundoplication, compared with 20% of patients after cholecystectomy. Oesophageal ileus is transient with subsequent return of pre-operative motility patterns (Chapter 2).   Of all patients undergoing laparoscopic antireflux surgery in the Unit (tertiary care hospital), the incidence of late revisional surgery is low at 5.6%, including 3% for persistent dysphagia. Dysphagia is the most common indication for revisional surgery, albeit with lower patient satisfaction with outcome than revisional surgery for recurrent reflux (Chapter 3).

In addition, flawed interaction between oesophageal and OGJ function is implicated in dysphagia. OGJ resistance to outflow is associated with dysphagia when there is sub-optimal distal oesophageal contractile strength and relatively high OGJ relaxation pressure on swallowing (Chapter 4). Limited tools for impedance-manometry data analysis inspired the conceptualisation and development of new automated combined pressure-flow analysis, achieved through scientific collaboration. This novel approach revealed for the first time that some patients have a pre-existing, asymptomatic, subtle variation of viscous bolus compression and movement in relation to oesophageal peristalsis that increases the risk of new-onset post-operative dysphagia (Chapter 5).

Fundoplication and hiatal repair alter OGJ anatomy to prevent reflux. However, after surgery, aberrant asymmetry of radial OGJ pressure during inspiration is associated with persistent dysphagia, consistent with a focally restrictive diaphragmatic hiatus from crural repair (Chapter 6).

In conclusion, oesophageal ileus in the early post-operative period is transient and the rate of late revisional surgery for troublesome dysphagia is low. Post-surgical dysphagia is related to a pre-existing pattern of sub-optimal bolus transport; and after surgery, inadequate modulation of oesophageal function in response to altered OGJ function. When antireflux surgery results in abnormally skewed OGJ pressures, dysphagia may be due to a 'snug' hiatal repair. Future studies hold promise for a reduction in post-surgical dysphagia through examination of local intrinsic modulation of swallowing function and development of objective calibration of hiatal repair.

THESIS DECLARATION

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution to Jennifer C Myers and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference had been made in the text.

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ACKNOWLEDGEMENTS

ABBREVIATIONS

3-D	Three-dimensional
AGA	American Gastroenterological Association
AIM	Automated impedance manometry
CFV	Contractile front velocity
DCI	Distal contractile integral
DRI	Dysphagia risk index
EAES	European Association of Endoscopic Surgery
Fr.	French size (external diameter) of the French gauge system
HRIM	High-resolution impedance manometry
HRM	High-resolution manometry
IBP	Intrabolus (or ramp) pressure
IQR	Interquartile range
IRP	Integrated relaxation pressure
LOS	Lower oesophageal sphincter
MCT	Multi-centred randomised trial
OGJ	Oesophago-gastric junction
PPI	Proton pump inhibitor
QoL	Quality of life
RCT	Randomised controlled trial
TGA	Therapeutic Goods Administration (Australia)
TLOSR	Transient lower oesophageal sphincter relaxation
US-FDA	Food and Drug Administration, U.S.A.
VAS	Visual analogue scale

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INTRODUCTION

1.1 OVERVIEW OF DYSPHAGIA AND ANTIREFLUX SURGERY

Dysphagia is defined as *'the perceived impairment of the passage of food from the mouth into the stomach'* (Vakil *et al.* 2006).[1] It is the most common adverse effect of antireflux surgery (Wills & Hunt 2001). Patients with dysphagia associated with surgical management of gastro-oesophageal reflux disease (hereafter reflux disease) are the focus of this research.

1.1.1 Symptoms interpreted as dysphagia

Patients most commonly report dysphagia when they feel swallowed material is sticking or passing sluggishly through the gullet. Other hallmark descriptors include chest or epigastric discomfort (AGA Medical Position Statement 1999; Cook 2008). The perceived impairment of bolus flow can arise anywhere between the posterior oral cavity and the stomach (Kuo *et al.* 2012). However, viscero-somatic referral makes a patient's perceived location of where a bolus is sticking unreliable (Roeder *et al.* 2004). Dysphagia is often not clearly defined for patients and some investigators confer additional meaning by assuming that bolus obstruction occurs. There seems to be some confusion between symptoms arising from mucosal hypersensitivity to bolus presence and symptoms associated with perceived resistance to bolus passage (see section 1.4.2).

1.1.2 Dysphagia before antireflux surgery

The focus of this thesis is dysphagia after antireflux surgery and its underlying pathophysiology. A complicating factor of this research is that dysphagia is often present prior to surgery. Many patients experiencing typical reflux symptoms, defined as weekly heartburn and/or regurgitation (Dent *et al.* 2005), also experience what they perceive as dysphagia. In some patients with gastro-oesophageal reflux, dysphagia resolves with antireflux medication (see section 1.4.2). For

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[1] Bibliography for Chapters 1 & 7 begins on p. 185

these reasons, baseline assessment of dysphagia prior to surgery is deemed critical and was undertaken prospectively for all patients included in this thesis.

1.1.3 Dysphagia after antireflux surgery

Post-operative or post-fundoplication dysphagia refers specifically to dysphagia that occurs as a consequence of antireflux surgery. This includes patients with new-onset dysphagia after fundoplication, as well as patients with clinically significant worsening of pre-existing dysphagia. Other adverse effects of antireflux surgery include inability to belch and bloating, but dysphagia is the most common of these (Gotley *et al.* 1996; Watson & Jamieson 1998; Triponez *et al.* 2005).

Dysphagia that is experienced immediately after antireflux surgery and up to six weeks afterwards is defined as early post-operative dysphagia. Early bothersome dysphagia is often transient and diminishes during this period. Dysphagia that continues or arises beyond 6 weeks after surgery is defined as late or persistent post-operative dysphagia (Hunter *et al.* 1996). Original research studies in this thesis explored separately the pathophysiology of early and late post-operative dysphagia.

Dysphagia after antireflux surgery is the focus of this clinical research because it reduces patient satisfaction with treatment, adversely impacts on quality of life and is a burden to the health-care system. Costly post-operative management includes medical consultations, investigations (manometry, radiology & endoscopy) and interventions (dilatation &/or re-operation)(Cowgill *et al.* 2007). Despite a thorough clinical review, in the majority of patients the mechanical basis of post-operative dysphagia is not identified (Furnee *et al.* 2009). Furthermore, with no pre-operative test reliably able to predict the development of post-operative dysphagia (Wijnhoven *et al.* 2008), surgeons are unable to anticipate who is at risk of this problem. In a nutshell, dysphagia after antireflux surgery is unpredictable, poorly understood and difficult to treat.

1.2   RECOGNITION AND GRADING OF DYSPHAGIA

There is no global consensus on dysphagia assessment. Since the inception of this thesis, regulatory authorities, such as the U.S. Food and Drug Administration (US-FDA) and professional bodies, have set general principles that are applicable for symptom-based assessments of medical conditions, in particular reflux disease (Stanghellini 2005; Dent *et al.* 2008). The generic US-FDA criteria include: content validity (measures the intended variable), construct validity (logical concept), internal consistency, test-retest reliability and ability to detect change (Estores 2014). The majority of dysphagia assessments currently in use are yet to be evaluated by these guidelines, as the large systematic studies required are costly and not of interest to sponsors such as pharmaceutical companies. Despite this, a few dysphagia instruments have proven to be effective.

1.2.1   Assessment tools for documenting dysphagia symptoms

1.2.1.1   Methods of assessment

There are two common approaches for documenting symptoms, those gathered by (i) investigator-assessment, and (ii) patient self-reported assessment. Symptoms recorded by a clinical investigator are open to investigator bias and considered inappropriate by the US-FDA. For instance, there is evidence that investigators underestimate the severity of symptoms experienced by patients (Dent *et al.* 2008). Also patients are commonly reticent at reporting poor outcomes directly to the clinician who provided the treatment. An alternative is an investigator not involved in the clinical process and blinded to treatment status, as it removes a source of observer bias (Watson & Lally 2009). The ideal is patient self-reported data (Stanghellini *et al.* 2007; Dent *et al.* 2008). In the studies conducted for this thesis, self-reported assessments were gathered prospectively at pre- and post- operative investigations.

1.2.1.2   Type of assessment

There are many types of questionnaires and response options in use for patient self-reporting of dysphagia symptoms. These include: (i) binary outcome (present/absent); (ii) verbal descriptors; (iii) multi-item rating scales, like the Likert scale; and (iv) a visual analogue scale (VAS), a numerical linear scale anchored at each end by the extremes of the dimension being measured (Guyatt *et al.* 1987; Nord 1991; Granderath *et al.* 2005). More in-depth specific dysphagia assessments include eating capacity assessments, such as the Composite dysphagia score (Dakkak & Bennett 1992) and the more recently developed Mayo Dysphagia Questionnaire 30-day (MDQ-30D)(McElhiney *et al.* 2010).

Screening questions using binary responses or simple descriptors can determine the presence or absence of swallowing difficulty. These responses can be used for internal consistency checks against more in-depth questions, but are of no value for discerning grades of dysphagia severity.

1.2.1.3   Grading severity of dysphagia

When evaluating dysphagia severity, consideration of bolus type is important. Dysphagia to solids is the most common problem after antireflux surgery, while surgery has little or no effect on the frequency and severity of dysphagia to liquids (Lafullarde *et al.* 2001). Thus it is paramount that questionnaires specifically evaluate difficulty with swallowing solids to enable identification of patients of interest.

There is no consistent definition and standard practice for recording dysphagia severity. Unfortunately, the consensus statement within the Montréal classification that 'troublesome dysphagia is present when patients need to alter eating patterns or report solid food impaction' (Vakil *et al.* 2006) is too vague to be useful for clinical research. Published studies show dysphagia severity is commonly graded by one of five methods, (i) categorically, by single word

descriptors (none, mild, moderate, severe)(Kamolz *et al.* 2000; Tsuboi *et al.* 2011); (ii) rated qualifying statements e.g. mild: aware but tolerable, moderate: discomforting, severe: incapacitating (Vakil *et al.* 2004), (iii) experience with certain bolus types, e.g. dysphagia with large pieces, small pieces, both food & drink (Funch-Jensen & Jacobsen 2007); (iv) grades that combine frequency and severity e.g. 'Grade 2: more than once a week, requiring dietary modification'(Tsuboi *et al.* 2011); or (v) retrospective grouping of VAS dysphagia scores e.g. score 1-3, mild; score 4-6, moderate; score 7-10, severe dysphagia (Lafullarde *et al.* 2001; Triponez *et al.* 2005).

It does not appear that any of these grading systems have been validated to ensure the severity score is an accurate measure of the dysphagia experienced during eating and drinking. It is unclear what grade of dysphagia can be referred to as significant dysphagia. Bessell *et al.* state "it is generally accepted that Grade 2 'bolus obstruction cleared by liquids' and Grade 3 'dysphagia for solids; need for dilatation; & bolus obstruction requiring admission' represent clinically significant dysphagia" (Bessell *et al.* 2000). However, while dysphagia to solids is common, whether bothersome dysphagia for solids after antireflux surgery is clinically significant dysphagia is a moot point. Few investigators clearly define clinically significant dysphagia. Assigning a dysphagia VAS score of 4-10 as 'troublesome dysphagia' seems to be an arbitrary decision (Watson *et al.* 1996; Baigrie *et al.* 1997). This topic has received little scrutiny. Clinically significant dysphagia after surgery will be examined in the studies of this thesis.

The widely used VAS incorporates a linear scale that ranges from 0 (none) to 10 (most severe) with one-unit divisions. It is attractively simple and helpful for detecting change across time or outcome for different treatments. This form of assessment has a high level of compliance and responsiveness, provides a numerical severity score and is able to detect small but important changes (de Boer *et al.* 2004). VAS, however, do not contain 'word pictures' for levels of severity. Word pictures are clarifying descriptors that enhance comprehension and responsiveness (Shaw 2004). Likert scales, that include a description for each level of severity,

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Table 1.1   Dysphagia assessment tool

Self-assessed dysphagia questionnaire

In the box below is a list of different types of food and drink. Please mark ($\checkmark$) the answer that is most applicable for each of the items listed. If you do not eat a particular item, your ability to eat a similar food should be scored.

Q: Do you have trouble with the following sticking as it moves down the gullet?

Swallowing ……….. is difficult	**Always**	**Sometimes**	**Never**
1. Water			$\checkmark$
2. Milk (thin soup)		$\checkmark$	
3. Custard (yoghurt, pureed fruit)		$\checkmark$	
4. Jelly			$\checkmark$
5. Scrambled eggs (baked beans, mashed potato)		$\checkmark$	
6. Baked Fish (steamed potato, cooked carrot)		$\checkmark$	
7. Fresh Bread (pastries)	$\checkmark$		
8. Apple (raw carrot)		$\checkmark$	
9. Steak (pork or lamb chops)		$\checkmark$	

Dysphagia (9 food types)

Scoring Table	Always	Sometimes	Never	Patient's Scores:	
1	1	0.5	0	Water	0
2	2	1	0	Milk	1
3	3	1.5	0	Custard	1.5
4	4	2	0	Jelly	0
5	5	2.5	0	Eggs	2.5
6	6	3	0	Fish	3
7	7	3.5	0	Bread	7
8	8	4	0	Apple	4
9	9	4.5	0	Steak	4.5

Dysphagia (9 food types)
calc: 0 - 45   23.5

Inset - Scoring table: 0 = *nil dysphagia*   to   45 = *dysphagia to all foods and drinks.*

Note: Scoring adapted from Dakkak & Bennett (1992). In our Unit, this composite dysphagia score is reversed from that originally described, so that the numerical score increases with a greater number and frequency of foods for which dysphagia is experienced (Watson *et al.* 1997).

have equally weighted, graded response options with a middle point (such as a 5-point scale: never, occasionally, sometimes, often, always). The use of word 'anchors' in Likert scales is considered by some experts to be better than a VAS that only defines symptoms at each end (always and never) (Guyatt *et al.* 1987; Dent *et al.* 2008). However, a Likert scale is not one item but a set of items or questions, the responses to which are added or averaged to produce a score. Unfortunately, Likert scales suffer from a central tendency bias and are difficult to validate (Uebersax 2006).

The recently validated MDQ-30D records the frequency and severity of dysphagia experienced in the previous 30 days, for foods of varying consistencies (McElhiney *et al.* 2010). It includes assessment of odynophagia (pain on swallowing) and behaviour modification e.g. pureeing and food avoidance. The MDQ-30D uses mixed formats: binary responses, Likert scales and multi-hierarchical items. It has undergone testing for concurrent validity (physician cf. self-assessed), internal consistency and reproducibility.

The Composite Dysphagia Score (Dakkak & Bennett 1992) documents difficulty with swallowing nine food types of increasing viscosity and solidity (water to meat; scale 0 – 45) (see Table 1.1). The components of the Dakkak and Bennett scoring system are weighted so that dysphagia for solids with increasing density and solidity receive progressively higher scores. The focus on bolus consistency is an important attribute in research for surgery-related dysphagia to solids. The inconsistent or day-to-day variability of dysphagia is accommodated by response options 'sometimes' and 'always'. Lastly, this is a well-validated instrument. Validation studies were undertaken within 7 days of subjects completing the questionnaire. Subjects were given a meal with all the food items assessed. An observer, unaware of the results of the questionnaire, scored the actual food eaten using the same scoring system. The strong correlation between subjects' perceived ability and investigator observed ability to swallow the 9 food types ($r = 0.79$, $p < 0.001$) means this assessment tool aids documentation of altered eating behavior and troublesome dysphagia.

Consideration was given to measuring the impact of dysphagia on quality of life (QoL) using the general 36-item Short Form Health Survey (SF-36) (McHorney *et al.* 1993) and the disease-specific GERD-HR-QoL (Koetje *et al.* 2016). However, the effects of antireflux surgery may have opposing impacts on QoL, with dysphagia having a negative impact and reflux control having a positive impact. In addition, QoL measures are affected by other co-morbidities and life experiences. For these reasons, QoL measures were not undertaken for studies in this thesis.

1.2.2   Influence of timing of dysphagia assessments before & after antireflux surgery

Dysphagia prevalence and severity differs between patients with treated and untreated gastro-oesophageal reflux disease. Dysphagia can be a presenting symptom in patients with uncontrolled acid reflux. Acid suppression therapy with a proton pump inhibitor (PPI) is now often trialled prior to investigations, which may reduce reflux and dysphagia symptoms (section 1.4.2) (Zschau *et al.* 2013). These factors can affect baseline dysphagia assessments prior to antireflux surgery.

There is no consensus on the best timing of dysphagia assessments. This likely contributes to the wide variation of the reported incidence of dysphagia both before and after surgery (Wills & Hunt 2001). For example, immediately after surgery, dysphagia is almost universally experienced (37/40, 93%) and lessens within 2-3 months (Funch-Jensen & Jacobsen 2007). For this reason, single studies that evaluate the same patients at different time intervals before and after surgery are most valuable.

1.2.3   Dysphagia assessment methods used in this thesis

The method and type of symptom assessments adopted for this thesis was informed by the literature on methods for assessing dysphagia to solids and an evaluation of our Unit's practices. The research projects presented in this thesis were conducted in a tertiary care hospital Unit.

The Visual Analogue Scale (VAS) has been used in this Unit since 1991 and the Composite Dysphagia Score developed by Dakkak & Bennett was adopted for routine use shortly thereafter (Watson *et al.* 1996). In this centre, both the Oesophageal Function Laboratory (research in this thesis) and the Laparoscopic Antireflux Surgery Assessment Unit use the same symptom assessment tools. Of the assessment tools outlined earlier (section 1.2.1.3), the MDQ-30D would be useful in this field of research. However this was not an option as the MDQ-30D was published after the commencement of studies for this thesis (McElhiney *et al.* 2010).

In the studies presented, VASs were utilised to assess symptom severity for dysphagia with solids and liquids. The frequency of dysphagia symptoms was reported using a rating scale (daily, weekly, monthly). Additionally, dysphagia severity and frequency were scored within the Dakkak & Bennett Composite Dysphagia Score for the difficulty of swallowing a range of foods (see Table 1.1). The frequency of other symptoms, such as heartburn, regurgitation and cough, were also self-reported using VASs. Dichotomous (yes/no) questions for each of these symptoms provided internal consistency and validity checks.

1.3   T OOLS FOR ASSESSING THE M ECHANICS OF D YSPHAGIA

1.3.1   Manometric systems and methods

Manometry is recommended for evaluation of dysphagia through assessment of the strength, speed and co-ordination of oesophageal muscle contractile function and patterns of oesophago-gastric junction (OGJ) relaxation during swallowing (AGA Technical Statement 2005). Manometric systems include: low-compliance water-perfused catheter systems with external pressure transducers (Arndorfer *et al.* 1977), and solid-state catheter systems with intraluminal pressure sensors (Ghosh *et al.* 2006). Both achieve high fidelity recording of intraluminal pressures at the sensor sampling point. Conventional 'low-resolution' manometry typically samples oesophageal luminal pressures at 3 - 5 cm intervals. More recently 'high-resolution manometry' (HRM) was developed to include a string of 16 - 36 closely spaced (1 - 2 cm) pressure sensors along a catheter. This development was advanced by computer-generated displays that enhance evaluation of topography of pressures (Ghosh *et al.* 2006). The Therapeutic Goods Administrator (TGA) in 2008 approved solid-state high-resolution manometry for use in Australia, which was after the commencement of studies for this thesis.

Water-perfused catheter systems were used to evaluate luminal pressures in original research presented in this thesis. Data were acquired at 40 Hz with commercial hardware and software, either the Gastromac (v3.3.5.3 Neomedix Systems, Sydney Australia) or Insight Acquisition system (Sandhill Scientific, Highland Ranch, CO, USA). These systems meet the standards recommended by the AGA Clinical Practice Committee (AGA Technical Statement 2005). Patients presenting for antireflux surgery who met study inclusion criteria, were invited to participate in the studies presented in this thesis. Manometric assessment excluded patients with known motility disorders associated with dysphagia such as achalasia, scleroderma oesophagus and diffuse oesophageal spasm (Mujica & Conklin 1999).

Studies in the 1970s established the refractory period for triggering oesophageal peristalsis after a preceding swallow (Ask & Tibbling 1980). In the same period, the utility of water swallows rather than 'dry' swallows was also established (Dodds *et al.* 1973). These developments helped inform the basic clinical manometry protocol in use world-wide, that is, a 5-10 minute rest period then ten, 5 mL water swallows each 30 s apart (Bredenoord & Hebbard 2012). This protocol was adhered to for routine manometric assessments of patients prior to surgery. However, this may not be the best protocol to evaluate surgery-related dysphagia.

Other parameters and other bolus types should better characterise changes in oesophageal function that are relevant to the pathogenesis of dysphagia, particularly after antireflux surgery. At the commencement of studies for this thesis there was only one published study using semi-solid or solids to evaluate dysphagia after antireflux surgery. Tatum *et al.*, in addition to a liquid barium bolus, used a 'marshmallow-like viscoelastic barium bolus' and recorded manometric pressures during fluoroscopic imaging of swallows undertaken in 12 patients after fundoplication compared to 20 healthy control subjects. Dysphagia scores after fundoplication correlated with longer OGJ transit for liquid and solid barium swallows, compared to normal subjects. The inclusion of the marshmallow-like bolus provided evidence that use of a viscous bolus could be standardised and was tolerated by subjects. Manometric variables of OGJ resistance to outflow were elevated by surgery, but did not relate to dysphagia in this study of a small sample size (Tatum *et al.* 2000).

There are occasional reports of manometric studies using other bolus types to evoke dysphagia symptoms in non-surgical patients, such as bread and more recently, apple sauce, to evoke dysphagia symptoms in non-surgical patients (Howard *et al.* 1989; Basseri *et al.* 2011). These studies conclude that a semi-solid or solid bolus reveals abnormalities of peristalsis not observed with liquid swallows. Bread swallows are difficult to standardise. A bread swallow may not be cleared from the oesophagus in a single swallow and its retention affects subsequent motor patterns. More studies are needed. The utility of a viscous bolus to assess dysphagia after

antireflux surgery is explored in studies of this thesis.

In addition to oesophageal body function, measuring OGJ pressure is an essential part of oesophageal manometry. For reasons that will be explained in subsequent sections, accurate measurement of residual OGJ pressure during swallow-induced relaxation is important in the assessment of the mechanics of surgery-related dysphagia. The AGA Technical Review on manometry states that intraluminal OGJ pressures need to be recorded using either a sleeve sensor or multiple closely spaced solid-state pressure sensors. These are the only methods that reliably record luminal OGJ pressure during axial movements of the OGJ, which occur during swallowing and respiration (AGA Technical Statement 2005). Unfortunately, some published studies report on OGJ function for pressure data derived from the invalid measurement approach of a single water-perfused side-hole. The sleeve consists of a 5-6 cm water-perfused membrane and is able to record OGJ pressure in the face of its mobility (Dent 1976). The sleeve sensor is used in several studies presented in this thesis. Our Unit transitioned to the use of HRM with intraluminal pressure transducers in 2009 – 2010, after commencement of the projects presented here.

The rarely used method of radial manometry, first described by Winans (Winans 1977), is used in this thesis to evaluate the radial variation of OGJ pressures after fundoplication. This involves a station pull-through of a water-perfused manometric catheter with multiple radially disposed side-holes (usually 4 - 8 at one level) to record both the axial and radial OGJ pressure.

1.3.2   Intraluminal impedance

The use of intraluminal impedance with concurrent manometry is an emerging measurement option, which can correlate luminal pressures with bolus movement. Impedance is recorded from multiple levels within the oesophagus with an intraluminal probe, consisting of a series of paired electrode rings, usually 2-cm apart. Impedance to an alternating electrical current across

pairs of electrodes is used to determine the nature of the oesophageal contents present at the level of each pair of electrodes (e.g. gas, liquid or empty oesophagus) (Silny 1991; Fass *et al.* 1994). Impedance has been available with diagnostic manometric systems for over 10 years, but remains largely a research tool due to the absence of proven clinical application. Initial published studies (see section 1.7.9.1) suggest the combined technology has potential for evaluating resistance to bolus passage as described by patients experiencing dysphagia. A study that applies novel data analysis method for combined impedance manometry data to evaluate dysphagia related to antireflux surgery is presented in this thesis.

1.3.3   Other technologies

A radionuclide oesophageal emptying test and a video-fluoroscopic barium swallow are other established tests capable of documenting oesophageal and OGJ passage of a test bolus. Radionuclide oesophageal emptying studies are limited by very low spatial resolution. Video-fluoroscopy has higher resolution and superior insight into the anatomy of interest. Both modalities involve ionising radiation that limits the number of swallows assessed. Certainly fluoroscopy is most valuable when acquisition is tailored to examine a specific question. However, for both modalities there is a lack uniformity of test bolus and rarely are they acquired in a structured manner. The findings of relevant studies conducted thus far will be discussed in section 1.7.9.1.

1.4 DYSPHAGIA ASSOCIATED WITH REFLUX DISEASE

1.4.1 Prevalence and severity of dysphagia in gastro-oesophageal reflux disease

Reflux disease has a reported population prevalence of 8.8 - 27.8% in western countries (11.6% in Australia), significantly higher than the 2.5 – 7.8% in East Asia (El-Serag *et al.* 2014). The Montréal classification defines reflux disease as 'a condition which develops when reflux of stomach content causes troublesome symptoms and/ or complications' (Vakil *et al.* 2006).

Dysphagia has a reported prevalence of 23 – 37% in patients with confirmed reflux disease (Vakil *et al.* 2004; Yates & Oelschlager 2015) and occurs in 20 - 54% of patients presenting for antireflux surgery (Wills & Hunt 2001). The figures may be high from inadvertent interpretation of odynophagia symptoms as dysphagia (see section 1.4.2 below).

The most cited publication on the severity of dysphagia in patients with reflux disease presents pooled data from several clinical trials that enrolled a total of 11, 954 patients with endoscopically confirmed mucosal breaks (erosive oesophagitis). At baseline, prior to randomisation to PPI therapies, 37% of patients reported dysphagia. In this sub-group of patients, dysphagia was mild but tolerable in 57%, moderate with discomfort in 32% and severe to incapacitating in 11% (Vakil *et al.* 2004). This shows that although what patients report as 'dysphagia' is highly prevalent in untreated reflux disease, severe dysphagia is rare. It should be noted though that this study did not specify whether dysphagia was to solids, liquids or both. Further the study was confined to patients with mucosal breaks, which represents about 30% of all patients with reflux disease.

In patients with reflux disease, dysphagia is most commonly experienced with solids. For patients consenting to antireflux surgery, dysphagia to lumpy solids (63%) is far more prevalent than soft solids (12%) or liquids (7%)(Watson *et al.* 1997; Chen & Orr 2005). These data steered

methods used in this thesis to emphasise assessment of dysphagia to solids both before & after surgery.

1.4.2   Impact of medical therapy on dysphagia associated with reflux disease

In the Vakil *et al.* study referred to above, 'dysphagia' resolved with acid suppression therapy in 83% of patients who reported dysphagia prior to PPI treatment (Vakil *et al.* 2004). This raises two important issues: a) patients appear to confuse dysphagia and odynophagia; and b) PPI therapy influences dysphagia assessments, particularly those made at baseline prior to surgery.

A review has noted that the distinction between dysphagia and odynophagia is often not well defined for patients undergoing surgery (Wills & Hunt 2001). In one study with clear definitions, odynophagia was more common before surgery and diminished after antireflux surgery (Watson *et al.* 1997). This factor may contribute to the variation in reports that 20 - 54% of patients experience dysphagia before antireflux surgery (Wills & Hunt 2001). In this thesis, 'dysphagia' has been clearly defined (section 1.1) to patients prior to self-assessment of symptoms.

1.4.3   Oesophageal motility and dysphagia in reflux disease

1.4.3.1   *Non-specific oesophageal motility disorders*

There is long-standing debate over the significance of so called 'non-specific motility disorders' which are motor patterns that do not match any known motility disorder or clinical syndrome (Spechler & Castell 2001). This 'disorder' has been variably defined. There is a wide range of manometric findings in patients with reflux disease from hypomotility to normal and even hypermotility. A non-specific motility disorder has been found in 23 - 36% of patients with reflux disease (Diener *et al.* 2001; Chan *et al.* 2011). Importantly though, the recognition of normal and disordered motility patterns may be sub-optimal, given that classification systems (Spechler &

Castell 2001; Kahrilas *et al.* 2015) are based on testing with a small liquid bolus.

1.4.3.2   Oesophageal hypomotility

Both the Spechler & Castell and the more recent 'Chicago classification' systems recognise the non-specific motility disorders of hypomotility or 'ineffective motility', the earlier system more consistently than the latter (Bowers 2015).   This is important, because a hypocontractile oesophagus (weak, absent or failed peristalsis) is the most prevalent finding in patients referred for manometry, accounting for 58% of assessments in one centre (Smout & Fox 2012).   However this pattern is not specific to reflux disease, as others have shown that hypomotility is common in patients with dysphagia unrelated to reflux disease (32%) (Conchillo *et al.* 2005).   With the exception of scleroderma oesophagus, the pathogenesis of hypomotility is unknown (Smout & Fox 2012).

It is controversial whether dysphagia is secondary to hypomotility in reflux disease (Lazarescu *et al.* 2010). In a recent study by Savarino *et al.*, 755 patients with reflux symptoms (heartburn and regurgitation) underwent motility and endoscopic assessments. In this study, hypomotility was called 'ineffective oesophageal motility' and defined when 30% of 10 water swallows had a peak peristaltic pressure of < 30 mmHg in the distal oesophagus. The proportion of patients with hypomotility increased in parallel with severity of reflux oesophagitis (mucosal damage) (Savarino *et al.* 2011).

In addition, defective secondary peristalsis [2] and hypomotility are associated with poor oesophageal clearance and thus prolonged distal oesophageal acid exposure.   Poor oesophageal clearance is associated with more severe reflux oesophagitis (Saraswat *et al.* 1994; Schoeman & Holloway 1995; Oberg *et al.* 1999; Diener *et al.* 2001; Somani *et al.* 2004; Ribolsi *et al.* 2014). Intriguingly, healed oesophagitis is not accompanied by improvement of oesophageal

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[2] *secondary peristalsis, peristalsis initiated in the oesophageal body that is not related to swallowing*

motility (Eckardt 1988). This suggests that inflammation arising from oesophagitis does not have a primary role in the pathogenesis of hypomotility (Fibbe *et al.* 2001). Rather, it seems that primary dysfunction of neural controls of oesophageal body motor function is the major contributor to hypomotlility.

1.4.4 Anatomical abnormalities of the OGJ in reflux disease

Anatomical abnormalities above, below and within the OGJ may lead to or exacerbate both reflux and dysphagia. Importantly, it is likely that an accumulation of abnormalities leads to a 'slippery slope' from normal to abnormal OGJ function, probably with more subtle degradations than have been acknowledged in the past (Boeckxstaens *et al.* 2014). Though the slippery slope of anatomical disruption of the OGJ probably impacts most on the antireflux capacity of the OGJ, such structural abnormalities may play a role in dysphagia in patients with reflux disease prior to surgery.

1.4.4.1 Structure of the normal oesophago-gastric junction

The normal OGJ consists of an intrinsic lower oesophageal sphincter (LOS) and the extrinsic crural diaphragm that surrounds the oesophagus (Figure 1.1). These are anchored together by the phreno-oesophageal ligament (Ingelfinger 1958; Bombeck *et al.* 1966; Mittal & Balaban 1997). Within muscle layers immediately distal to the LOS are the opposing gastric sling and clasp fibres of the gastric cardia (Liebermann-Meffert *et al.* 1979), which may be a part of the functional LOS (Brasseur *et al.* 2007). Gastric sling fibres generate greater tone than clasp fibres (animal study, porcine)(Farre *et al.* 2007). Sling fibres create the angle of His[3] and may contribute to a flap valve mechanism. The OGJ flap valve as described by Hill *et al.* is said to be present when pressure in the gastric fundus creates a flap that presses against the lower end of the oesophagus to prevent reflux (Hill *et al.* 1996). However the absence of this flap in subjects

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[3] angle of His, *deepest angle between the oesophagus and fundus formed by the acute angle of insertion of the sling fibres in the gastric cardia, named in honour of Wilhelm His Jr.* (Friedland 1978; Liebermann-Meffert *et al.* 1979)

with hiatus hernia suggests that sling fibres alone do not account for the appearance of a gastric flap.

Immediately proximal to the LOS is an area referred to by radiologists as the phrenic ampulla (Friedland 1978). This term is used to describe the transient change in shape of the distal oesophagus from a tubular to globular shape when filled with a bolus. It is proposed this facilitates transfer of a swallowed bolus between the tubular oesophagus and stomach, possibly through co-ordinated interaction of circular and longitudinal smooth muscle function of the distal oesophagus and the OGJ (Kwiatek *et al.* 2012).
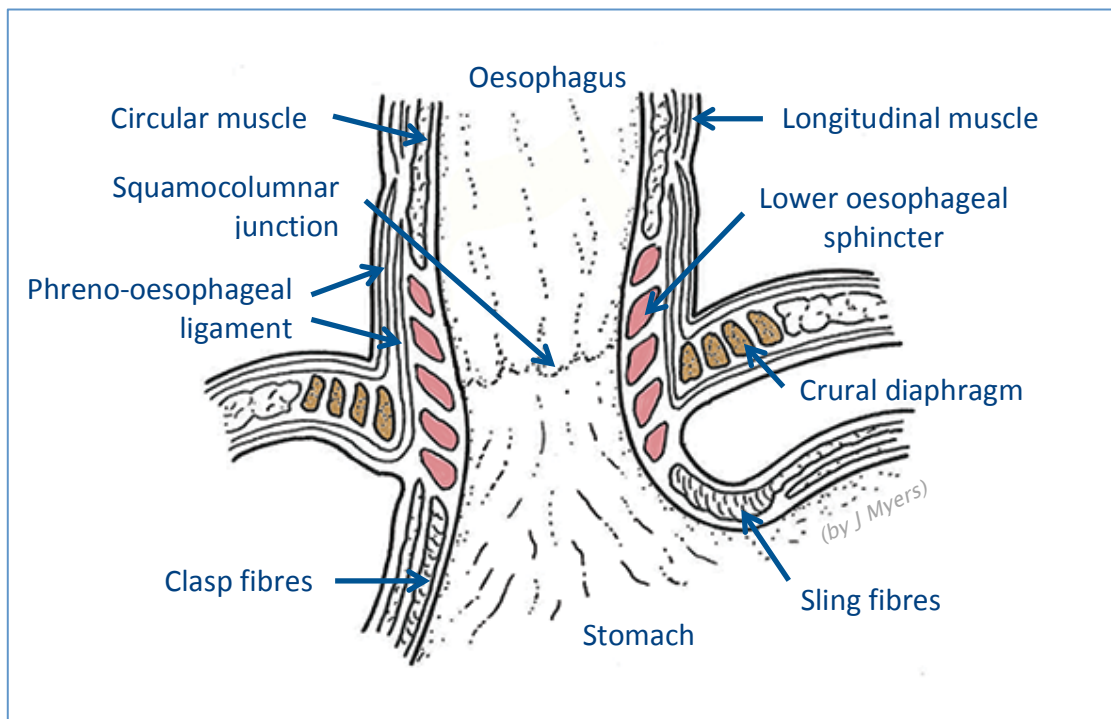
Figure 1.1   The oesophago-gastric junction (OGJ).

The internal lower oesophageal sphincter and the external crural diaphragm are superimposed and anchored to each other by the phreno-oesophageal ligament.

1.4.4.2   Separation of OGJ components and formation of hiatus hernia

Varying criteria are used to define and classify hiatus hernia (Fuchs *et al.* 2014). It is generally agreed that a hiatus hernia is present if there is at least a 2 cm axial separation between the LOS and crural diaphragm (Gordon *et al.* 2004). This rather loose and anatomically crude definition reflects the difficulty of defining and detecting herniation. When herniation occurs, several elements of the antireflux barrier are compromised: the crural diaphragm is misaligned; the phreno-oesophageal ligament is defective; the angle of His is diminished; and the LOS is displaced into the thorax. This anatomical abnormality can be detected on endoscopy, fluoroscopy or low/high resolution manometry. Concordance between modalities is poor (Khajanchee *et al.* 2012; Koch *et al.* 2014), not least because of different criteria for hernia presence and type with each modality, but also because sliding hernias can spontaneously reduce or be missed during testing (Mittal 1997; Roman & Kahrilas 2015).

The most widely used classification grades hiatus hernia based on the LOS position and the laxity of the phreno-oesophageal ligament. Type I is a sliding hernia, with circumferential laxity and the OGJ is above the diaphragm. Type II is a para-oesophageal hernia, in which the LOS is below the diaphragm, but localised laxity results in a portion of the stomach sliding above the diaphragm and next to the oesophagus. Type III, is a combination of OGJ and stomach above the diaphragm, with large hiatal hernia or intra-thoracic stomach (≥30 or ≥50% stomach in chest) sometimes called Type IV (Gordon *et al.* 2004; Canon *et al.* 2005). Type I, sliding hiatus hernia with intermittent herniation of the gastric cardia, is the most common (72- 85%) and frequently found in reflux disease patients (50- 60%)(Petersen *et al.* 1991; Kahrilas 1993; Khajanchee *et al.* 2012).

The anatomical origin or specific point of change that defines when a hiatal hernia begins to form is disputed (Gryglewski *et al.* 2014). Regardless, the presence of a hiatus hernia means the LOS and crural diaphragm no longer act synergistically for effective bolus transport, nor work

together to prevent reflux. Thus this anatomical variation has functional consequences. Although not the focus of this thesis, it is noted that patients with a hiatus hernia are more likely to experience heartburn and regurgitation (Petersen *et al.* 1991) in proportion to hiatus hernia size (Franzen & Tibbling 2014). Oesophageal acid exposure is more often abnormal in reflux patients with a hiatus hernia than without (time with oesophageal pH < 4 = 7.6% *vs.* 3.3%, p<0.01), giving rise to the current thinking that hiatal hernia is a key underlying pathogenic factor for reflux disease rather than a co-incidental anomaly (Murray & Camilleri 2000; van Herwaarden *et al.* 2000; Boeckxstaens *et al.* 2014). This assessment is supported by a study of patients with an intermittent hiatus hernia. When herniation was present there was twice as much reflux compared to when it was absent (23.1% *vs.* 12.2%, p<0.05) (Bredenoord *et al.* 2006). Further, it is not just the presence of a hiatus hernia, but the abnormal position and function of the crural diaphragm that contributes to the malfunction of the antireflux barrier in patients with reflux disease (van Herwaarden *et al.* 2000).

1.4.4.3   Impact of hiatal hernia on OGJ function and dysphagia

Hiatus hernia is the most commonly recognised abnormality of the OGJ (Gordon *et al.* 2004). The greater the size of hiatus hernia, the more likely dysphagia is to occur (Kohn *et al.* 2013). Patients with hiatal hernia have delayed acid clearance (Emerenziani *et al.* 2006), partly from entrapment of reflux within the hernia (Mittal *et al.* 1987) and partly from a flaccid oesophagus resulting in diminished peristaltic vigour (Kahrilas *et al.* 1995). 'Dysphagia' may be associated with perception of contents above or within the hiatus hernia. Oesophageal bolus hold-up or retrograde flow is significantly more prevalent in Type I hiatal hernia patients with dysphagia than those without (64% *vs.* 33%, p<0.04) (Kaul *et al.* 1990). A notable flaw of many studies evaluating dysphagia in reflux patients prior to antireflux surgery is that data are not presented separately for patients with & without a hiatus hernia (Chew *et al.* 2011; Raue *et al.* 2011; Marjoux *et al.* 2012). The impact of type I hiatal hernia on dysphagia and objective measures are reported in this thesis.

1.4.4.4 Impact of hiatal laxity on OGJ function and dysphagia

An aspect often overlooked with regard to OGJ luminal pressure and function is the influence of the crura of the diaphragmatic hiatus. The mechanical characteristics of the hiatal opening and the hernia characteristics are both likely to be important in reflux disease and dysphagia. Prior to antireflux surgery, a hypotensive OGJ pressure may be the result of low pressure from the internal lower oesophageal sphincter and/ or a low-pressure contribution from the extrinsic crural diaphragm due to hiatal laxity, irrespective of the presence or absence of a hiatus hernia.

Antireflux surgery was initially designed to only treat the hiatus hernia, which at the time was considered the major cause of reflux disease (Allison 1951; Stylopoulos & Rattner 2005). This highlights that for surgeons, the altered hiatal anatomy with widening of the hiatal canal/ oesophageal hiatus is a key focus of the operation (Koch *et al.* 2014). Their interest is well placed, because although rarely measured, the intraoperative size of the oesophageal hiatus correlates significantly with the degree of abnormal reflux and conversely with luminal OGJ resting pressure (Batirel *et al.* 2010). Unfortunately outside the operating room, hiatal laxity is not easily or routinely assessed and validated criteria for grading hiatal laxity at endoscopy are lacking (Dent *et al.* 2012).

The impact of hiatal laxity on dysphagia is unclear. During swallowing, contraction of the oesophageal longitudinal muscles transiently elevates the OGJ (Kahrilas *et al.* 2008). One study has demonstrated with combined manometry/fluoroscopy, that OGJ elevation and duration of migration (time to recoil) is markedly longer during transient lower oesophageal sphincter relaxation (TLOSR) compared to LOS relaxation of swallowing (4.3 cm *vs.* 1.2 cm, p= 0.002; 23.6 sec *vs.* 6.9 sec, p = 0.003). They proposed that this migration and recoil of the OGJ as the mechanism for genesis of a hiatus hernia (Lee *et al.* 2012). However, the role of hiatal laxity and migration/ recoil of the OGJ with regard to dysphagia requires investigation.

1.5 ANTIREFLUX SURGERY

1.5.1 Principles of antireflux surgery

The major principles of antireflux surgery are: (i) to dissect the OGJ area and position the LOS in the abdomen; (ii) reduce any hiatal hernia; (iii) suture the crura to correct hiatal laxity and to realign the crural diaphragm with the LOS; (iv) re-create the angle of His; and (v) wrap the fundus around the end of the oesophagus to support the intrinsic LOS (Figure 1.2) (Seely *et al.* 2005).

1.5.2 Evolution of antireflux surgery

Rudolph Nissen & Bernard Dallemagne first described the techniques to achieve the principles of antireflux surgery for open and laparoscopic fundoplication respectively (Nissen 1956; Dallemagne *et al.* 1991). Several aspects of these operations were modified and standardised, to minimise technical errors and technical failures. Development of partial fundoplication arose out of the belief that a plication of lesser radial extent would lower the incidence of post-operative dysphagia. The most common variations that have evolved out of this mostly empirical process are:

- Total 360° (Nissen, after Rudolph Nissen, 1956): total posterior fundoplication with (Dallemagne *et al.* 1991) or without division of the short gastric vessels (Jamieson *et al.* 1994) (Figure 1.2);

- Posterior 270° (Toupet, after André Toupet, 1963): a posterior partial 270° plication; intra-abdominal fixation of the fundus to the hiatal pillar (Cuschieri *et al.* 1993) (Figure 1.3);

- Anterior 180° (Dor, after Jacques Dor, 1967): an anterior 180° fundoplication; with fixation of fundus to left & right hiatal pillars (Watson *et al.* 1999b) (Figures 1.3 & 1.4).

- Anterior 90° ('anatomical', after Philip Allison, 1951): anterior 90° fundoplication; with fixation of fundus to apex of angle of His and left hiatal pillar (Krysztopik *et al.* 2002) (Figure 1.4).

❖ Hiatal repair

- o Reduce hiatal hernia

- o Repair hiatal defect (illustrated)

(Illustration by J Myers)
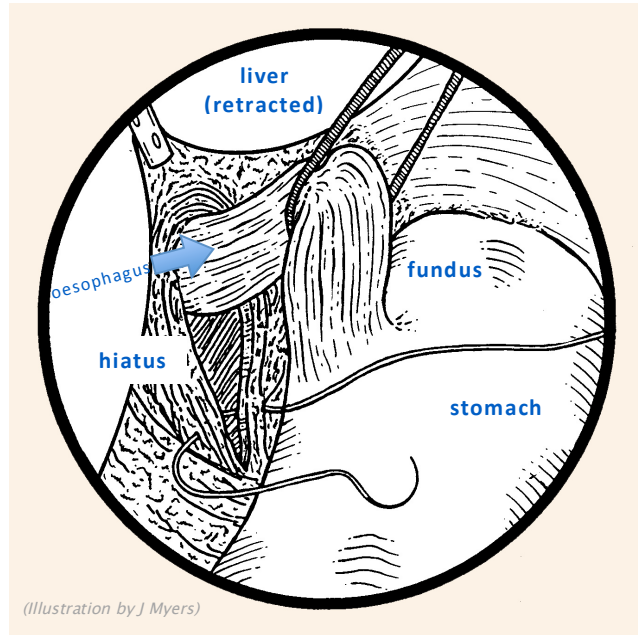
❖ Fundoplication

- o Re-create the angle of His

- o Increase intra-abdominal oesophageal length

- o Position the lower sphincter near crura

- o Create fundal wrap (illustrated)

(Illustration by J Myers)
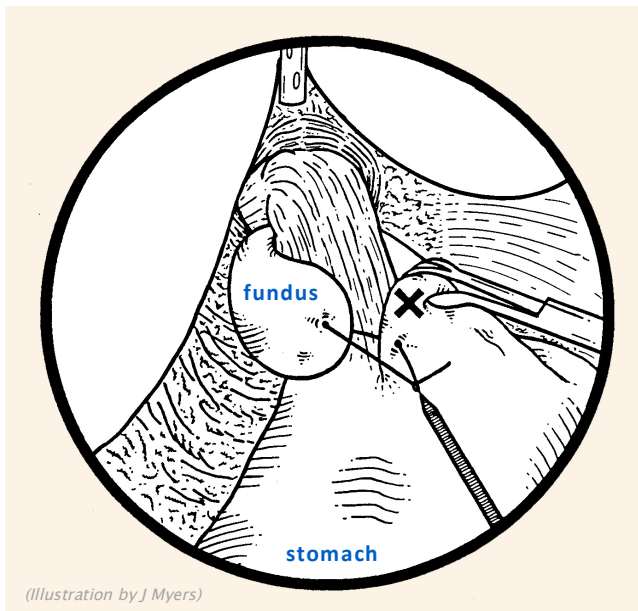
Figure 1.2   The main principles of Laparoscopic Antireflux Surgery.

Worldwide, a total plication, a Nissen using the anterior and posterior walls, or Nissen-Rossetti, using only anterior wall of the fundus, is the most common operation (Stylopoulos & Rattner 2005).

1.5.3 Tensions between reflux control and prevention of dysphagia

The choice of fundoplication type performed is influenced strongly by local practice. There is tension between optimising reflux control and minimising dysphagia risk. Total 360° fundoplication is the most reliable for reflux control (Fisichella & Patti 2014) and the most common operation type in the U.S.A. A posterior 270° fundoplication is favoured on the European continent, and 180° and 270° fundoplication are performed frequently in Australia.

The value of operator experience in determining outcomes is gaining recognition. This is reflected in the practice guidelines of the European Association of Endoscopic Surgery (EAES) and Esophageal Diagnostic Advisory Panel U.S.A., which states 'the choice of which fundoplication should be determined by the individual surgeon according to his/her experience' (Jobe *et al.* 2013; Fuchs *et al.* 2014).

In each of the following sub-sections, 1.5.4 to 1.5.8 is a short description of a modification to operative technique that has been adopted with a view to reducing dysphagia risk. A review of the impact of these techniques on patient outcomes and insights into pathophysiology of surgery-related dysphagia follows thereafter.

1.5.4 Reduction of axial extent of fundoplication

The original total fundoplication as described by Rudolph Nissen involved grasping the posterior wall of the fundus from behind the oesophagus, to wrap it around 6cm of the distal oesophagus and suturing it to the anterior wall of the fundus using 4 - 5 sutures (Nissen 1956; Jamieson &

Deschamps 1988). Post-operative dysphagia was unacceptably high and it was thought the wrap was 'too long and too tight' (Kim & Velanovich 2014). DeMeester *et al.* proposed that extensive mobilisation of the fundus, shortening the wrap length to 1-2 cm (formerly 5cm) and formation of this wrap over an intra-oesophageal bougie would reduce post-operative dysphagia (DeMeester *et al.* 1986). These steps were also adopted for the laparoscopic approach (Watson & Jamieson 1998).   These changes create what is now referred to as a short and loose 'floppy' fundoplication.

1.5.5   Variation of radial extent of fundoplication

The history of laparoscopic surgery is briefly described elsewhere (Thompson & Watson 2015), but the upshot is post-operative dysphagia has been the driver of change leading to the development of fundoplication of lesser radial extent. It is under appreciated that different types of fundoplication in terms of circumferential extent, have varying concomitant technical elements to achieve the principles of antireflux surgery (section 1.5.2 and Figures 1.3 & 1.4). These may impact on surgery-related dysphagia.

1.5.6   Intra-oesophageal bougie use during formation of fundoplication

It is often debated whether an intra-oesophageal bougie placed across the OGJ during formation of fundoplication helps reduce the risk of post surgery dysphagia. Nissen used a 36 French (Fr.) bougie for this purpose, but DeMeester advocated use of larger bougie, up to 60 Fr. diameter. While use of a 52 – 56 Fr. bougie is often reported in the literature, a survey of German surgeons in 2005 revealed only 46% use a bougie during this part of the operation (Jarral *et al.* 2012).

(Illustration by J Myers)

Dor 180º anterior   **Toupet 270º posterior**   **Nissen 360º total**
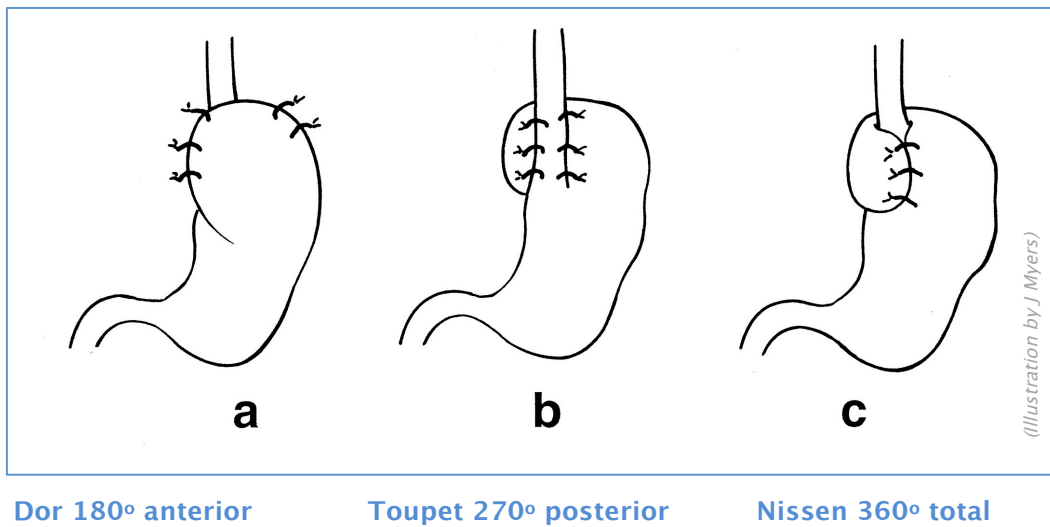
Figure 1.3   **Most common types of fundoplication.** For each type, the fundus covers a varying degree of the OGJ circumference and it is adhered differently to the oesophagus and repaired oesophageal hiatus.

90° fundoplication:

(Illustration by J Myers)

180° fundoplication:

(Illustration by J Myers)
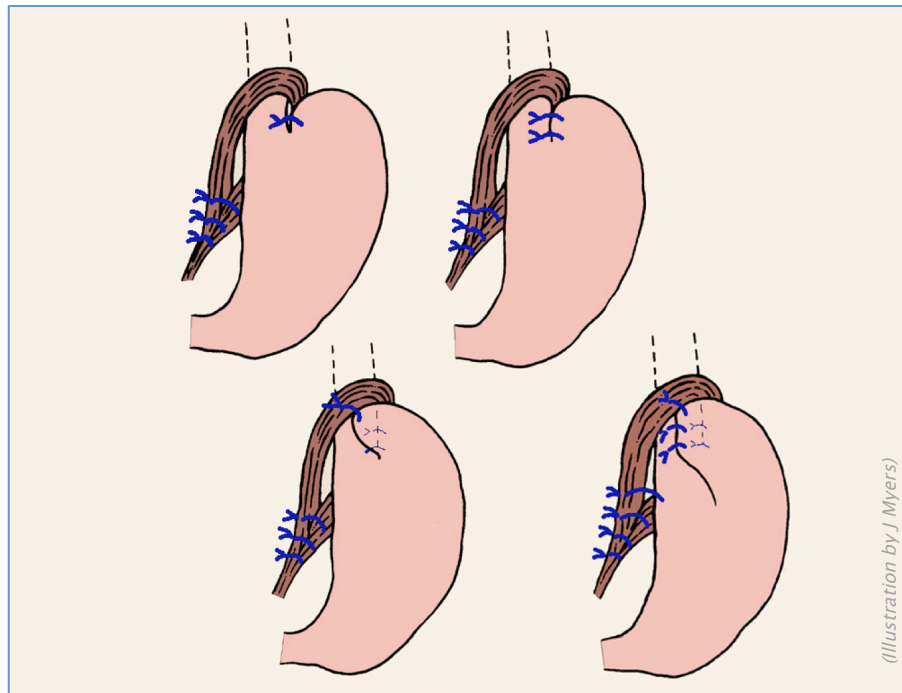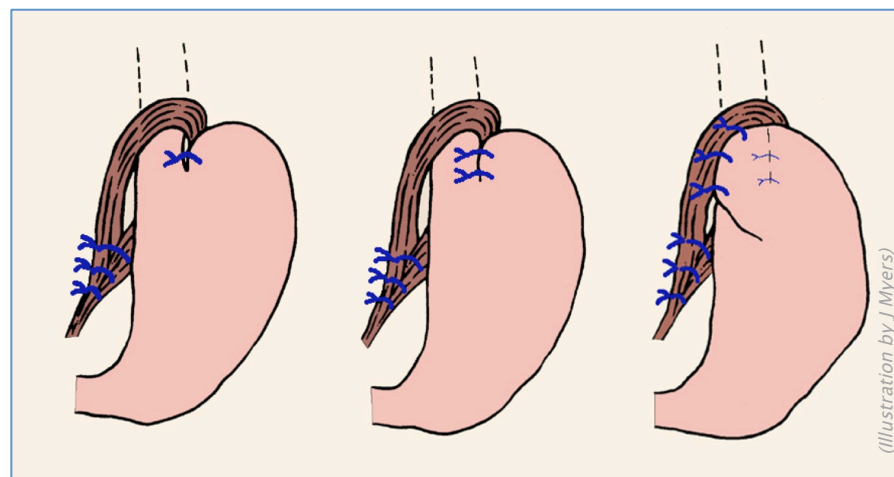
Figure 1.4   **Anterior partial fundoplication.** The first two steps recreate the angle of His, after which a partial 90° (top image) or 180° (bottom image) anterior fundoplication is created.

1.5.7   Division of short gastric vessels

During fundal mobilisation for a total plication the short gastric blood vessels from the lower margin of the spleen to the greater curve of the stomach can be divided. The risks and benefits of this step remain controversial. Some consider this an essential technical element for a floppy, tension-free fundoplication (Patti et al. 1998), while others do not (Schijven et al. 2014). Dividing these vessels results in longer operating times and the extensive dissection elevates the risk of intra-operative bleeding and splenic infarction (Markar et al. 2011).

1.5.8   Techniques of hiatal repair

With the advent of laparoscopic surgery, surgeons focused on techniques for an optimal fundal wrap and paid less attention to hiatal repair (Wijnhoven *et al.* 2008). Initially hiatal repair was reserved for patients with a hernia or a wide hiatal defect (Cuschieri *et al.* 1993). In our Unit, hiatal repair was infrequent between 1991-1993, but the occurrence of para-oesophageal herniation (6.7%) altered practice and crural repair is now routine (Watson *et al.* 1995a; Watson *et al.* 1995b). It is now agreed that closure of the hiatus is an essential part of surgery, primarily to avoid herniation (Horgan *et al.* 1999).

A number of variations of technique for hiatal repair may be relevant to post-operative dysphagia, including the:

- Method of hiatal dissection e.g. diathermy or blunt dissection;

- Choice of an anterior or posterior repair of the crura;

- The degree of hiatal narrowing and number of stitches needed to achieve this;

- Use of an intra-oesophageal bougie to calibrate the size of the oesophageal hiatus

- Use of prosthetic reinforcement of the hiatus to prevent intra-thoracic migration/ herniation.

1.6   EARLY POST-OPERATIVE DYSPHAGIA

1.6.1   Definition and clinical significance

As previously stated (section 1.1.3), dysphagia experienced up to six weeks after antireflux surgery is defined as early post-operative dysphagia. Post-operative care is critical. Anti-emetics are standard in the first 24 hours as retching may disrupt the new antireflux barrier leading to dysphagia and/or reflux. Oral fluids are commenced on the evening of surgery and if tolerated, a soft diet is introduced the next day (Khan *et al.* 2009). In some centres the latter is allowed only after a contrast swallow confirms a sub-diaphragmatic position of the fundoplication (Tsunoda *et al.* 2010). Discharge instructions usually include the advice of adopting a diet consisting of soft foods and liquids for 6 weeks after surgery to minimise troublesome dysphagia.

1.6.2   Incidence and natural history

A study incorporating a daily dysphagia diary shows dysphagia can occur as early as day-1 after antireflux surgery. This is often 'bothersome' with dysphagia for some foods either 'a few times a day' or 'always' in the first month (37/40, 93%). It usually subsides or resolves within 5 - 6 weeks of surgery (Funch-Jensen & Jacobsen 2007), a finding supported by Kamolz *et al.* (Table 1.2)(Kamolz *et al.* 2000). Other studies reporting findings at 4 - 6 weeks after surgery suggest fundoplication of less than total radial extent and/or technical elements, like full fundal mobilisation with division of short gastric vessels, reduced severe early dysphagia to solids. However these conclusions were not firmly based on objective data (Hunter *et al.* 1996; Alexander *et al.* 1997).

Table 1.2   Short-term Dysphagia Severity after Laparoscopic Nissen Fundoplication, N = 87

Grade of Dysphagia	Before Surgery	1 week after surgery	6 weeks after surgery	3 months after surgery
None	92 %	50.6 %	73.6 %	80.5 %
Mild	8 %	18.4 %	13.8 %	16.6 %
Moderate	0 %	14.9 %	8.0 %	4.6 %
Severe	0 %	16.1 %	4.6 %	2.3 %

Grade of dysphagia, verbal rating scale 'swallowing difficulties: none, mild, moderate, severe'

Adapted from: Kamolz T, Bammer T and Pointner R. Predictability of dysphagia after laparoscopic Nissen fundoplication. *Am J Gastroenterol* 2000; 95: 408-414 *(Kamolz et al. 2000).*

In the early post-operative period, severe dysphagia requiring intervention is uncommon. Rates of endoscopic dilatation of the OGJ are low, ranging from 0 – 5% (Lafullarde *et al.* 2001; Wills & Hunt 2001; Makris *et al.* 2012).   Early re-operation rates for dysphagia range from 2.8 - 4% (Yau *et al.* 2000; Tsunoda *et al.* 2010).

1.6.3   Pathogenesis

Early post-operative dysphagia can arise from technical errors at surgery or technical failures (anatomical disruptions) precipitated by early post-operative vomiting (Patti *et al.* 2015). These anatomical abnormalities, which are not the focus of this thesis, include: (i) herniation of the fundoplication and OGJ; (ii) para-oesophageal herniation; (iii) malposition or bi-lobed stomach; or (iv) slipped fundoplication, whereby the OGJ and hiatus hernia are above the diaphragm, but the fundoplication remains below the diaphragm (Richter 2013).

In the absence of anatomical abnormalities (described above), early dysphagia in the first 6 weeks after surgery is often attributed to the surgery-induced oedema of the OGJ (Funch-

Jensen & Jacobsen 2007; Richter 2013). Use of diathermy at surgery, less tactile feedback and a learning curve may be other contributing factors associated with the laparoscopic approach (Watson & Jamieson 1998). Tissue damage caused by diathermy may result in scarring (Watson *et al.* 1995a; Le Blanc-Louvry *et al.* 2000). Thus use of scissors and blunt dissection of tissues has been recommended to reduce dysphagia due to hiatal stenosis (Watson *et al.* 1995a).

Does manipulation of structures around the OGJ disturb tissue and motor function? The literature is bereft of mechanistic studies on early dysphagia. The only known study in an animal model (English abstract; published in Portuguese), found a significant correlation between histologically assessed oedema of the distal oesophageal tissue from histology and weight loss at day 2 & 7 after 360° fundoplication (Wistar rats, N=70)(Rocha *et al.* 2004). The impact of antireflux surgery on oesophageal motility and OGJ function in the early post-operative period is unknown and is the focus of a study presented (Chapter 2).

1.7   LATE POST-OPERATIVE DYSPHAGIA

1.7.1   Definition and clinical significance

Dysphagia that continues or arises beyond 6 weeks after antireflux surgery is defined as late or persistent post-operative dysphagia.   Clinical presentation includes an impaired ability to consume solid foods because of dysphagia, with the use of liquids to clear foods.   Less commonly, dysphagia is associated with weight loss and bolus obstruction. The management of patients with late post-operative dysphagia is complex and not well codified (Patti *et al.* 2015). The EAES consensus recommends investigations (endoscopy, fluoroscopy, manometry & reflux testing) of patients seeking treatment of dysphagia with the aim of identifying the underlying mechanical factors (Fuchs *et al.* 2014).   The consensus did not recommend any tailoring of manometric testing methods to this clinical problem.   Endoscopic evaluation and, if deemed appropriate, endoscopic dilatation is common practice. Patients with persistent dysphagia are offered further surgery if conservative management with dietary modification and dilatation fails or improvement is short-lived (Richter 2013).

1.7.2   Prevalence and natural history

Various elements of surgical technique may impact on the prevalence of late dysphagia after anti-reflux surgery, so these are reviewed in detail in sections 1.7.4 – 1.7.10.

Few studies provide a reliable picture of the impact of time on the prevalence of late dysphagia. Single-centre studies are needed that follow the same patients at specific time intervals after the same type of antireflux surgery, using the same dysphagia assessment instrument, including documentation of dysphagia to solids. Two randomised controlled trials (RCTs) were identified that fit these criteria, but their findings were conflicting.   In both centres, dysphagia was documented before and after surgery using the Dakkak & Bennett Composite Dysphagia Score

Table 1.3   Long-term dysphagia outcome

A single RCT comparing anterior partial fundoplication and posterior total fundoplication, with multiple long-term follow-up time points

RCT, South Africa		Dysphagia assessments		
Time after surgery Leading author, year	Fundoplication type	No dysphagia	Dysphagia to solids Mean VAS score (95% CI)	Dakkak & Bennett Score Mean (95% CI)
3 months post-op Baigrie *et al*, 2005	180° Anterior 360° Total	52 % 33 %	1.2 (0.8 - 1.7) 2.4 (1.9 - 2.9)	5.0 (3.4 - 6.6) 9.8 (7.7 - 12.0)
12 months post-op Baigrie *et al*, 2005	180° Anterior 360° Total	77 % 58 %	0.4 (0.2 - 0.7) 1.0 (0.7 - 1.4)	1.0 (0.4 - 1.7) 3.5 (2.0 - 4.9)
24 months post-op Baigrie *et al*, 2005	180° Anterior 360° Total	95 % 74 %	0.1 (0.0 - 0.2) 0.6 (0.3 - 1.0)	0.2 (0.2 - 0.4) 1.1 (0.5 - 1.7)
RCT, single centre randomised controlled trial; VAS, visual analogue score (range 0 -10), 95% CI, 95% confidence interval.				

Table compiled from source document (Baigrie *et al.* 2005). Data from a single RCT, i.e. same patient group assessed at different time intervals after surgery

Table 1.4   Extended follow-up with long-term dysphagia outcome

A single RCT comparing anterior partial fundoplication and posterior total fundoplication, with multiple long-term follow-up time points

RCT, South Australia		Dysphagia assessments		
Time after surgery Leading author, year	Fundoplication type	No dysphagia	Dysphagia to solids Mean VAS score (95% CI)	Dakkak & Bennett Score Mean (SD)
6 months post-op Watson *et al*, 1999	180° Anterior 360° Total	85 % 60 %	0.6 (0.1 - 1.0) 1.1 (0.6 - 1.6)	2.1 (0.89) 4.2 (0.89)
5 years post-op Ludemann *et a*l, 2005	180° Anterior 360° Total	NR NR	1.5 (NR) 2.6 (NR)	6.5 (NR) 11.4 (NR)
10 years post-op Cai *et al*, 2008	180° Anterior 360° Total	66 % 48 %	1.7 (NR) 2.4 (NR)	7.8 (5.3) 12.0 (4.2)
RCT, single centre randomised controlled trial; NR, not reported; VAS, visual analogue score (range 0 -10), 95% CI, 95% confidence interval, SD standard deviation.				

Table compiled from source documents *(Watson et al. 1999b; Ludemann et al. 2005; Cai et al. 2008).* Data from a single RCT, i.e. same patient group at different time intervals after surgery

questionnaire (see page 8, Table 1.1). In each RCT, patients were randomised to undergo either 180° anterior or 360° total fundoplication (Watson *et al.* 1999b; Baigrie *et al.* 2005). In the Baigrie *et al.* study (Table 1.3), the number of patients reporting no dysphagia increased and mean dysphagia severity scores decreased at each follow-up time point (3 mo, 12 mo, 24 mo) for both operations (Baigrie *et al.* 2005). These data contrast with the findings of the Watson *et al.* study (Table 1.4), where the number of patients reporting no dysphagia decreased and the dysphagia severity scores increased between 6 months and 10 years for the both operation types.

It is difficult to explain these conflicting findings. In the Baigrie *et al.* study, one surgeon performed all operations and outcome for heartburn was similar for both operations at each follow-up. In the Watson *et al.* study, several surgeons performed operations and heartburn scores increased over time. A limitation of both RCTs was reliance on subjective outcomes. It is speculative, but not unreasonable to suggest technical elements of surgery and/or operative durability was different between the two centres. More studies with uniform time and methods of assessment are needed.

1.7.3   Relationship between early and late post-operative dysphagia

An issue given little attention in the literature is the relationship between early (<6 weeks) and late dysphagia (≥ 6weeks). There are at least four groups of patients with dysphagia after antireflux surgery, those with: (i) pre-operative dysphagia that is unchanged post-operatively; (ii) pre-operative dysphagia that worsens post-operatively; (iii) new-onset early post operative dysphagia related to surgery, that diminishes or remains similar in the long-term; and (iv) late complications of surgery, that give rise to dysphagia. In addition, any of the above patients may have an underlying factor that manifests as a result of antireflux surgery and precipitates or elevates post-operative dysphagia.

Markris *et al.* specifically studied patients after laparoscopic 360° fundoplication (with crural repair, division of short gastrics, 2cm-long total wrap created over large bougie) to determine the long-term outcome of those with and without early dysphagia at 3 weeks after surgery (N= 423; 398 respectively). Patients consumed pureed food for 2 weeks after surgery.   At 3 weeks after surgery, dysphagia to solids and liquids was assessed separately with a grading system that combined frequency and severity e.g. Grade 1: mild dysphagia, experienced once or twice/ month; Grade 4: very severe dysphagia, experienced with ever swallow. At this time, patients were classified into the early dysphagia group (dysphagia score: 1–4) or 'no early dysphagia' group (dysphagia score: 0). Of patients with early dysphagia, 45% experienced late dysphagia at or beyond 6 months after surgery. Of patients free of dysphagia at 3 weeks after surgery, 25% experienced late dysphagia. When sub-classified by the degree of severity of early dysphagia, patients with moderate & severe early dysphagia had significantly higher late dysphagia scores than those with no early dysphagia ($p<0.001$), though the mean severity score was low (<1 out of 4 i.e. mild dysphagia). Endoscopic dilatation was required similarly for patients with & without early dysphagia (4.5% *vs.* 3.5% respectively).   Only three patients from the 'early dysphagia' group required revisional surgery for troublesome late dysphagia (3/423, 0.7%)(Makris *et al.* 2012).

This study suggests that, (a) the absence of early post-operative dysphagia does not preclude the occurrence of late dysphagia, with the latter speculatively associated with the re-introduction of a regular diet; and (b) revisional surgery for dysphagia was rarely required. Post-operative dysphagia that is mild or bothersome is a management dilemma and problematic given the pathogenesis of dysphagia is unknown. The cause remains to be elucidated and will be explored in the studies presented (Chapters 3 - 6).

1.7.4   Influence of length of fundoplication

Remarkably, there is little in the way of robust evidence that reducing the length of fundoplication reduces post-operative dysphagia, though this is a plausible concept. DeMeester *et al.* published surgical outcome for dysphagia for a series of patients with 4cm, 3cm and 1cm long fundoplication, stating: "shortening the length of fundoplication decreased the incidence of persistent dysphagia from 21% to 3 %, $p<0.01$" (DeMeester *et al.* 1986). However it should be noted the authors introduced multiple changes (bougie size, fundus mobilisation, wrap length) within and across four time periods of a consecutive patient series with learning curve bias and no randomisation of patients. In this study, dysphagia was defined as 'any discomfort in swallowing' that was temporary (resolved within < 3 months) or persistent, but it is unclear if patients were reporting dysphagia to solids, liquids or both. Dysphagia severity was unfortunately not recorded. On closer inspection of this study, the reported reduction in persistent dysphagia could equally be attributed to fully mobilising the gastric fundus prior to forming the fundoplication. Manometric data in this study was invalid (single side-hole pressure, see section 1.3.1; and pooled data for all operation types).

Physiological studies provide more robust evidence that reduction of fundoplication length should reduce the risk for development of dysphagia. The length of fundoplication was found to influence the manometric length of the OGJ high-pressure zone as determined by low- or high-resolution manometry (Kahrilas *et al.* 2000; Scheffer *et al.* 2005). The relationship between OGJ/fundal canal length and post-operative dysphagia is less clear. In one study, OGJ length was not different between those with and without persistent dysphagia after total fundoplication (Bais *et al.* 2001). Scheffer *et al.* used combined HRM-fluoroscopy to show that total fundoplication increased OGJ length and diminished OGJ opening diameter, resulting in a narrower, elongated OGJ outflow tract than before surgery. Also this prospective small study of 12 patients, found that after surgery a longer bolus transit time through the OGJ correlated with

Table 1.5 **Details of RCTs comparing types of anterior fundoplication with types of posterior fundoplication for dysphagia after surgery**

Antireflux operation						Follow-up at 3- 6 months	
Leading author, year location, trial type	n	Method plication	Degrees plication	Bougie at plication	†Fixation to oesophagus	Dyphagia to Solids (% Yes)	Dakkak & Bennett Score Mean (SD)
Watson *et al*, 1999 Australia, RCT	54 53	Anterior Posterior	180 360	None 52 Fr.	Yes No	15 % 40 %	2.1 (0.89) 4.2 (0.89)
Hagedorn *et al*, 2003 Sweden, RCT	47 48	Anterior Posterior*	120 180-200	None None	Yes Yes	NR NR	5.5 (1.2) 7.2 (1.6)
Watson *et al*, 2004 Australia, MCT	60 52	Anterior Posterior*	90 360	None 52 Fr.	Yes No	14 % 22 %	3.2 (0.79) 7.5 (1.81)
Chrysos *et al*, 2004 ‡ Greece, MCT	12 12	Anterior Posterior	180 360	None None	Yes No	NR 25 %	-
Baigrie *et al*, 2005 ¥ South Africa, RCT	79 84	Anterior Posterior	180 360	NR 56 Fr.	No No	NR NR	5.0 (NR)** 9.8 (NR)**
Spence *et al*, 2006 ‡ Australia, RCT	40 39	Anterior Posterior	90 360	None 52 Fr.	Yes No	63 % 69 %	2.23 (2.92) 11.74 (4.8)
Khan *et al*, 2010 UK, RCT	53 50	Anterior Posterior	180 180	None None	Yes Yes	11 % 13 %	-
RCT, single centre randomised controlled trial; MCT, multicentre randomised controlled trial; Degrees plication, indicates the circumferential extent of fundoplication; Bougie, use of intra-oesophageal bougie during fundoplication; Fr., French; NR, not reported; †Fixation of fundoplication to the oesophagus, *Division of short gastric vessels, ‡follow-up between 3-6 months after surgery, ¥follow-up at 3 months after surgery, ** review tabulated 24-month data, modified to include 3-month data.							

Table adapted from two systematic reviews *(Memon et al. 2015)* and *(Broeders et al. 2011)* with additional data obtained from source documents *(Watson et al. 1999b; Hagedorn et al. 2003; Chrysos et al. 2004; Watson et al. 2004; Baigrie et al. 2005; Spence et al. 2006; Khan et al. 2010). Footnote:* Data from the meta-analyses is not included due to inappropriate pooling of patient data for different types of operations.

greater post-operative dysphagia to solids and liquids. This relationship was not present prior to surgery (Scheffer *et al.* 2005).

1.7.5   Influence of radial extent of fundoplication

The highly variable dysphagia scores at ~6 months after antireflux surgery for fundoplication of varying radial extent are summarised in Table 1.5. These data were drawn from published studies that: documented dysphagia outcome for the presence and severity of dysphagia to solids; prospectively evaluated patient outcomes at predefined time-points after surgery; clearly described the surgical technique undertaken; assigned patients by random allocation to operation type; and were published in a peer-reviewed journal. The most limiting factor of this filter of published studies was adequate dysphagia assessment. However, of seven randomised control trials that met the above criteria, six utilised the Dakkak & Bennett Composite Dysphagia Score. In these studies all patients underwent a crural repair; 3/7 trials were double-blinded (patient & assessor) and all had common primary outcome measures i.e. post-operative dysphagia and heartburn. Table 1.5 highlights that there is considerable variation in operative technique and outcome at different centres. Even a subset of RCTs comparing the same two types of fundoplication by radial extent, 180° *vs.* 360° (Watson, Chrysos and Baigrie) utilised different technical elements during surgery (± use bougie; ± fixation of plication to the oesophagus).   The mean and spread (standard deviation from the mean) of dysphagia scores is considerable, although it is noted that within each centre partial fundoplication of ≤180° radial extent had lower prevalence and severity of dysphagia to solids than fundoplication of ≥180° radial extent.

It is still widely debated whether division of the short gastric blood vessels is necessary during mobilisation of the fundus to create a floppy, tension-free fundoplication to minimise dysphagia. This matter should be put to rest, as a systematic review and meta-analysis of 3 RCTs found no statistically significant influence on risk for dysphagia at 1 and 5 years after surgery (Khatri *et al.*

2012).

A number of RCTs have assessed the influence of radial extent of fundoplication on outcome. RCTs have compared 270° *vs.* 360° (7 RCTs) and 180° *vs.* 360° (5 RCTs). There is one multi-centre randomised trial (MCT) that compared 90° *vs.* 360° fundoplication. Systematic reviews and meta-analyses of common outcome measures indicate each operation has its own outcome profile (Broeders *et al.* 2010; Nijjar *et al.* 2010; Broeders *et al.* 2013). Adverse effects of surgery such as dysphagia, gas bloat, increased flatulence and inability to belch are most common with complete fundoplication and less prevalent with fundoplication of lesser radial extent. For example, at 12 months after 360° fundoplication, a patient is 1.6 times more likely to experience post-operative dysphagia than after 270° posterior fundoplication (relative risk, RR 1.61, p<0.02), and is also at greater risk of being unable to belch (RR 2.04, p= 0.009) and experience more gas bloat (RR 1.58, p<0.001), yet both operations have similar reflux control (Broeders *et al.* 2010). Whereas at 12 months after 90° fundoplication, a patient is 2.5 times *less* likely to report dysphagia for solids than after 360° fundoplication (0.21: 0.52, p= 0.001), but is at greater risk of recurrent or uncontrolled reflux (p=0.04)(Nijjar *et al.* 2010). Risk of post-operative recurrent reflux has an inverse relationship with fundoplication radial extent. Thus there is debate about the suitability and durability of partial fundoplication in patients with severe reflux disease e.g. Barrett's oesophagus (Horvath *et al.* 1999; Wong *et al.* 2008; Nijjar *et al.* 2010).

One mechanism by which fundoplication radial extent may impact on risk for dysphagia is reduction of OGJ compliance caused by the fundal wrap. DeMeester suggested that use of a large bougie during formation of the fundal wrap helped maintain the OGJ luminal opening. This conceivably minimises the impact of fundoplication on restricting OGJ compliance, thereby lowering the risk of persistent post-operative dysphagia (DeMeester *et al.* 1986). A blinded RCT assigned 171 patients to use or non-use of a 56 Fr. bougie during fashioning of a 360° fundoplication. At 11 months after surgery, in the group in which the bougie was used, fewer patients experienced troublesome dysphagia than in the non-use group (late dysphagia of any

severity 17% *vs.* 31%, p = 0.047; severe dysphagia 5% *vs.* 14%, p = 0.06 respectively)(Patterson *et al.* 2000). The small risk (0.8%) of oesophageal perforation from use of a bougie seems justified by these data (Jarral *et al.* 2012).

Fluoroscopic imaging of barium-opacified liquid or solid boluses passing through the OGJ have shown that fundoplication reduces OGJ luminal opening diameter after both 360° (Kahrilas *et al.* 1998; Scheffer *et al.* 2005) and 180° fundoplication (Anderson *et al.* 1998). These findings indicate fluoroscopy is a useful method to assess OGJ opening diameter and flow and potentially dysphagia. Unfortunately these studies either assessed patients with little or no dysphagia (Kahrilas *et al.* 1998) or were inadequately powered (small sample size) to fully assess the relationship between OGJ opening diameter and severity of dysphagia in patients after antireflux surgery.

1.7.6 Manometric indicators of abnormal OGJ resistance to bolus flow

The following two manometric measures quantify pressures associated with OGJ function, thus are important in research about the mechanics of early and late post-operative dysphagia.

1.7.6.1 Residual OGJ relaxation pressure

It has been shown that prior to fundoplication there is virtually complete effacement of OGJ pressure during swallowing. After fundoplication, complete effacement is lost, so there is measurable residual OGJ pressure during swallow-induced relaxation (Dent *et al.* 1982; Kiroff *et al.* 1984). This led to the proposal that incomplete OGJ relaxation pressure, and not OGJ resting pressure, was the main mechanism of antireflux action of fundoplication. These two studies focused on the mechanism of antireflux action by fundoplication and did not address the relationship between incomplete OGJ relaxation and post-operative dysphagia to solids.

A subsequent prospective study with a specified follow-up protocol, found residual OGJ pressure after Nissen fundoplication was significantly higher at 3 months and 2 years after surgery in patients with moderate and severe dysphagia compared to those with none or mild dysphagia (p= 0.017, p= 0.004 respectively) (Scheffer *et al.* 2004). Furthermore, Bais *et al.* reported that a reduction of residual OGJ relaxation pressure was associated with resolution of dysphagia symptoms in patients who underwent revisional surgery for dysphagia (Bais *et al.* 2001). Most recently, a HRM study of 20 patients evaluated before and 2-3 months after Nissen-Rossetti fundoplication found that integrated relaxation pressure (IRP, HRM equivalent of residual OGJ relaxation pressure) was significantly higher in 8 patients with dysphagia compared to 12 patients without (10 mmHg *vs.* 5 mmHg, p<0.02)(Marjoux *et al.* 2012).

There are very few studies that investigate the influence of fundoplication radial extent on residual OGJ relaxation pressure. A low-resolution manometric evaluation of patients at 3-months after surgery, found that median residual OGJ relaxation pressure was greater after 360° fundoplication than after 180° fundoplication (17.0 *vs.* 6.5 mmHg respectively, p= 0.016). Furthermore, residual OGJ relaxation pressure weakly correlated with dysphagia to solids (r=0.37, p= 0.04)(Anderson *et al.* 1998). A comparative manometric study of 270° fundoplication and 120° fundoplication did not report on residual OGJ relaxation pressure (Hagedorn *et al.* 2003). A comparison of 360° and 90° fundoplication in 112 patients found a trend toward more complete OGJ relaxation with swallowing after an anterior 90° wrap (5.0 *vs.* 2.4 mmHg respectively, p= 0.06), but a relationship with dysphagia was not evaluated (Watson *et al.* 2004). The impact of fundoplication on residual OGJ relaxation pressure is explored further in the studies of this thesis (Chapters 4 & 5).

1.7.6.2   Intrabolus pressure

Intrabolus pressure, also referred to as ramp pressure, is the pressure rise that occurs within the oesophageal body as a result of the presence of a swallowed bolus. The advancing oesophageal

peristaltic wave drives the progressive compression of the bolus in the distal oesophagus above the OGJ. Thus the ramping up and plateau of bolus pressure is most prominent in the distal oesophagus (Ingelfinger 1958). Intrabolus pressure plateaus when the pressure has risen to the level of pressure required to overcome resistance to flow across the OGJ during swallowing. Thus the peak or plateau of intrabolus pressure reflects the resistance of the OGJ to the passage of a bolus into the stomach.

A retrospective analysis of 103 patients who underwent manometry both before and 3 – 6 months post-operatively, found intrabolus pressure doubled after 360° fundoplication (10.5 to 20.5 mmHg, p <0.0001). Mean intrabolus pressure after surgery was significantly different between patients with moderate or severe dysphagia to liquids compared to patients with none or mild dysphagia (10.1 to 13.2 mmHg, p <0.04), but this measure did not correlate with dysphagia for solids (Mathew *et al.* 1997). Perhaps in this study there were too few patients with moderate/ severe dysphagia to solids (14%) compared to liquids (20%).

A further study by Anderson *et al.* found that total 360° fundoplication elevated intrabolus pressure significantly more than partial 180° fundoplication (26 *vs.* 21 mmHg, p<0.03). This suggests that altering radial extent of fundoplication has a measurable effect on OGJ distensibility and resistance to passage of a bolus. Pooling of data for 180° and 360° fundoplication in this study revealed a weak correlation between dysphagia for solids and intrabolus pressure (r= 0.37, p = 0.04)(Anderson *et al.* 1998).

These tantalising data on intrabolus pressure and post-operative dysphagia are possibly inconclusive because they evaluated small volume liquid boluses. As emphasised earlier, dysphagia to solids is a common feature of late post-operative dysphagia. An exploration of factors that affect intrabolus pressure and its relationship to dysphagia is presented in this thesis (Chapters 4 & 5).

1.7.7   Relevance of conventional measures of OGJ resting pressure

Antireflux surgery has repeatedly been shown to elevate OGJ resting pressure (Hill 1978; DeMeester *et al.* 1986; Wills & Hunt 2001). However, OGJ resting pressure, as recorded with water-perfused sleeve or HRM, does not correlate well with dysphagia after antireflux surgery (Mathew *et al.* 1997; Scheffer *et al.* 2004; Marjoux *et al.* 2012).

1.7.8   Assessment of radial patterns of OGJ resting pressure

Measurement of radial pressure patterns across the OGJ enables documentation of luminal pressures in three-dimensions and holds promise for better understanding of OGJ mechanics before and after antireflux surgery. It has long been established that both the LOS (Liebermann-Meffert *et al.* 1979; Liu *et al.* 1997) and crural diaphragm are anatomically and mechanically asymmetrical (Bradley *et al.* 2015).

Three-dimensional (3-D) mapping of luminal OGJ pressures as described by Winans (Winans 1977), was used in a pioneering study by Bombeck *et al.* who found both the pressure and length of the OGJ were less in patients with reflux disease than in control subjects. After Nissen fundoplication, 3-D pressure profiles were similar to those for normal control subjects, a finding confirmed by others (Bombeck *et al.* 1987; Kahrilas *et al.* 2000).

Although it is often overlooked, both LOS and crural diaphragm pressures vary during swallowing and respiration (Mittal *et al.* 1988; Mittal *et al.* 1995). Further, the crural diaphragm can contribute to a high-pressure zone in the absence of a LOS after oesophago-gastrectomy (Klein *et al.* 1993). Thus measurement of OGJ pressure according to phase of respiration may be helpful in elucidating hiatal mechanics, especially in patients with post-operative dysphagia.

Despite the potential of radial pressure measurements for revealing OGJ mechanics, there are no studies that evaluate 3-D OGJ pressure in patients with and without dysphagia after antireflux surgery. Such measurements require a manometric catheter dedicated to measurement of radial pressures and a specialised measurement protocol. Chapter 6 of this thesis presents a study of radial OGJ pressure before and after antireflux surgery, according to dysphagia status (Chapter 6).

1.7.9   Oesophageal body peristaltic function

The impact of fundoplication on oesophageal motor function is unclear and the relationship between oesophageal peristalsis and post-operative dysphagia is inadequately described. Fibbe *et al.* randomised 200 patients with and without pre-operative dysmotility[4] to either 270° or 360° fundoplication to assess the impact of radial extent of fundoplication on oesophageal function and dysphagia. After surgery, oesophageal peristalsis remained unchanged in 85% of patients and some patients of both groups experienced post-operative dysphagia (31% of the 'normal motility' group and 30% of the 'dysmotility' group). Severe dysphagia (product of severity and frequency scores) causing considerable discomfort was reported after both types of surgery in a minority of patients (3/100 patients, 360°; 4/100 patients, 270°). The authors commented that dysphagia for solids was not always associated with dysmotility and concluded that low-resolution manometry was insufficiently sensitive to evaluate dysphagia (Fibbe *et al.* 2001). However, in this study 90% of new-onset dysphagia was mild or moderate, thus it is likely that the target group of interest (severe dysphagia) were too few in number for adequate analysis.

HRM defines more clearly the contractile segments of oesophageal peristalsis and the transition zone between the proximal (striated) and distal (smooth) oesophageal muscle (Kahrilas *et al.* 2015). Thus HRM offers potential for better discrimination of features of peristalsis relevant to dysphagia. It's been shown with HRM, that patients with dysphagia are more likely to have large

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[4] *dysmotility defined as <40% peristalsis &/or distal contraction amplitude < 40mmHg for ten, 5mL water swallows*

peristaltic breaks (>20% swallows with >5 cm breaks in 20 mmHg isocontour) (Roman *et al.* 2011). However, large peristaltic breaks are also present in patients with reflux disease and hypomotility (*defined as distal contractile integral DCI < 450 mmHg/s/cm, a measure of contractile vigour combining contractile amplitude, duration and axial length*)(Xiao *et al.* 2012; Ribolsi *et al.* 2014). In a study to establish normal HRM values after fundoplication (dysphagia patients excluded), smaller peristaltic breaks were found following 360° compared to 270° fundoplication (p<0.05), but it is unclear if these were present beforehand due to the use of conventional low-resolution manometry prior to surgery (Weijenborg *et al.* 2015).

Two studies report HRM studies before and after antireflux surgery. A Toyko based study focused on the antireflux properties of the 270° fundoplication and did not evaluate dysphagia status with manometric measures of oesophageal peristalsis (Hoshino *et al.* 2015). A study from Lyon, France, found measures of oesophageal body function (DCI and CFV, contractile front velocity cm/s) did not significantly differ between 8 patients with and 12 patients without dysphagia at 2-3 months after 360° fundoplication. Dysphagia was graded with a 4 point Likert-type scale (none to severe), although it is unclear if this was dysphagia for solids and/or liquids. Of the 8 patients with dysphagia, only one patient reported severe dysphagia (mild in 5, moderate in 2). Pooling of data and a low patient numbers were major limitations of this study (Marjoux *et al.* 2012).

Thus far, studies exploring the effect of fundoplication on oesophageal body motor function and correlates with dysphagia are lacking both power and rigour. The inter-relationship of the strength, speed and co-ordination of oesophageal contractions of peristalsis and measures of OGJ function, such as intrabolus pressure and residual relaxation pressure, have not been adequately assessed with regard to surgery-related dysphagia. This formed the focus of the study presented in Chapter 4.

1.7.9.1   Oesophageal peristalsis and bolus transport

Information about bolus flow through the oesophagus and OGJ is a likely linchpin to understanding dysphagia. Chrysos *et al.* randomised 33 patients with impaired peristalsis (mean distal contraction amplitude <30 mmHg) to either 270° or 360° fundoplication. Fluoroscopy was utilised to assess oesophageal transit using a standard protocol before and 3 months after surgery. For both types of surgery, oesophageal transit of a 15 mL barium-coated bread bolus was significantly slower and more pronounced in patients with progressively more severe dysphagia, when compared to pre-operative transit (39 *vs.* 30 sec, p= 0.001, 270°; 49 *vs.* 32 sec, p= 0.02, 360°). Intriguingly, the authors state the bread bolus stagnated in the mid-distal oesophagus of these patients, not near the OGJ. The authors proposed that dysphagia results from anatomical distortion of the distal oesophagus by the fundal wrap, but provided no objective evidence to support this view (Chrysos *et al.* 2003). Unfortunately, bolus flow time through the oesophagus and OGJ were not documented separately, which would have aided a better understanding of oesophageal peristaltic propulsion and OGJ resistance to flow in patients with and without post-operative dysphagia.

Combined impedance–manometry has been used to evaluate oesophageal bolus transport and dysphagia. A protocol has been developed using 5mL saline and 5mL conductive viscous bolus (jelly) swallows (Tutuian *et al.* 2003). An impedance-manometry assessment was undertaken in 80 consecutive patients evaluated at least 4 months (range 4 – 148 months) after fundoplication. The study included patients treated with variants of fundoplication, but 85% had a 360° Nissen fundoplication. Measures of peristalsis[5] were not different between patients with and without dysphagia.   Yet patients with incomplete bolus clearance, revealed by the impedance measurements, were more likely to report dysphagia (61% *vs.* 32%, p =0.01). The authors concluded that impedance can detect disorder of oesophageal bolus transport not detected by manometry (Yigit *et al.* 2006). Of note though, the data analysis was suboptimal, as patients

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[5] *conventional manometry: Normal peristalsis: ≥ 70% swallows with distal peristaltic amplitude > 30 mmHg; velocity < 8cm/s; Ineffective peristalsis: >30% swallows amplitude <30mmHg, velocity ≥ 8cm/s).*

with dysphagia of any severity were placed in the dysphagia group. Further, it is unknown if incomplete bolus clearance was present in patients prior to surgery, as no pre-operative data were available.

Montenovo *et al*. performed pre- and post-operative impedance-manometry studies in 74 patients treated with laparoscopic 360° fundoplication. Dysphagia with a severity of ≥4 (VAS 0-10 scale) occurring at least one/month was reported by 13 of 74 patients after surgery, but of these, only 3 patients had new-onset dysphagia. By contrast with the study of Yigit *et al*., at a mean 18 months (range 6 - 46 mo) after surgery, success of peristalsis and bolus transport (clearance) did not significantly differ between those with and without surgery-related dysphagia. The only predictor of post-operative dysphagia was the presence of pre-operative dysphagia (Montenovo *et al*. 2009). A limitation of both studies was the variable timeframe of assessment, 4 – 148 months after surgery.

It appears that regardless of modality for assessing bolus transport, current measures of oesophageal motility, bolus transport and dysphagia do not correlate well. Are the right measurements being made? Although impedance and pressure data are acquired concurrently, there have been no tools for second-by-second (data point-by-data point) correlation of impedance and manometry data. This was a missed opportunity for analysis development in past-published studies. This was the impetus for a study using impedance-manometry before and after fundoplication, including a fortuitous collaboration and a new approach to data analysis (presented in Chapter 5).

1.7.10   Contribution of hiatal repair

Only one study has evaluated the mechanical effects of hiatal repair alone on OGJ pressure (Louie *et al*. 2013). This intra-operative HRM study randomised 18 patients to either undergo hiatal repair first or fundoplication first. 'Hiatal repair first' augmented OGJ pressure by a mean

of 10.2 mmHg, which contrasted with '360° fundoplication first', in which OGJ pressure rose by a mean of only 3.5 mmHg (p = 0.07). This finding while not statistically significant suggests that hiatal repair has substantial impact on OGJ pressure, a concept that is alien to most thinking about OGJ pressure after antireflux surgery. Post-operative dysphagia assessments were not included in this study.

It is likely that both hiatal repair and fundoplication contribute to a reduced OGJ opening diameter and thus impact on OGJ residual relaxation pressure and distal oesophageal intrabolus pressure. In support of this, a concurrent fluoroscopic-manometric study 6 months after 360° fundoplication in 7 patients free of dysphagia by Kahrilas *et al.*, found a flow-limiting constriction at the level of the hiatus along with significantly reduced OGJ axial mobility and a smaller OGJ luminal opening diameter compared to controls and patients with hiatus hernia. Further, intrabolus pressure was higher and OGJ transit of a marshmallow more frequently required multiple swallows after 360° fundoplication (Kahrilas *et al.* 1998). These findings suggest that closing the hiatal defect and securing the fundoplication to prevent herniation, affects both the OGJ compliance and mobility. It seems that hiatal repair and fundoplication together reduce OGJ relaxation and opening diameter and also limit OGJ axial mobility, which normally occurs during swallowing when contraction of oesophageal longitudinal muscles transiently elevates the OGJ (see section 1.4.4.4).

The reduction of axial OGJ mobility associated with hiatal repair and fundoplication probably varies amongst surgeons and operative techniques, as various methods are used for fixation of the fundal wrap on the oesophagus, stomach, and/or hiatal rim. There are no known studies addressing whether the degree or extent of fixation around the hiatal rim affects surgery-related dysphagia.

1.7.10.1 Anterior or posterior hiatal repair

The diaphragmatic hiatus can be repaired in front of or behind the oesophagus. An anterior repair is easier to perform and leaves the oesophagus in its native position. By contrast, a posterior repair may better preserve intra-abdominal oesophageal length, but this approach may abnormally angulate the distal oesophagus (Jamieson *et al.* 1994). Speculation over whether anterior or posterior hiatal repair are associated with a greater risk for post-operative dysphagia has been addressed by a RCT. In this RCT, 102 patients were randomised to either anterior or posterior hiatal repair that was completed over a 52 Fr. bougie and followed by a Nissen fundoplication. The authors reported that there was no difference between the two types of hiatal repair for dysphagia scores at 6-month after surgery. However this does not adequately reflect the most relevant clinical outcome of this study, as several patients required a second operation prior to the 6-month dysphagia assessment. Notably, within the first 6 months, there were more re-operations for troublesome dysphagia after posterior than anterior repair (11/55 *vs.* 2/47, p= 0.011)(Watson *et al.* 2001). It is probably more appropriate to conclude that in this trial, posterior hiatal repair was more commonly associated with severe dysphagia that required re-operation.

1.7.10.2 Mechanical calibration of hiatal repair

The greatest difficulty in researching the role of hiatal repair in post-operative dysphagia is that hiatal repair is not standardised, is frequently not calibrated and is performed differently in many studies (Fein & Seyfried 2010). The placement of a large diameter bougie within the oesophago-gastric lumen during hiatal repair is routine in some centres but not in others. Where a bougie is used, the size varies greatly from 32 - 60 Fr. The use of a bougie is not without risk, as perforation of the anterior oesophageal wall can occur (Watson & Jamieson 1998; Jarral *et al.* 2012). Methods of calibration of hiatal repair and their effect on post-operative outcome with regard to dysphagia warrant systematic study.

1.7.11   Insights about dysphagia from revisional surgery

Primary antireflux surgery has a failure rate 10 - 15%. Surgical revision is undertaken in about 3 - 6% of patients following primary surgery for either recurrent reflux or troublesome dysphagia (Fuchs *et al.* 2014). Revisional surgery is more difficult than primary surgery owing to distorted anatomy, peri-hiatal scarring and adhesions (Watson *et al.* 1999a). There are limited reports from individual centres, including ours, of the findings and short-term outcomes of revisional surgery. These report on small patient numbers and one fundoplication type (Watson *et al.* 1999a; Coelho *et al.* 2004; Papasavas *et al.* 2004; Ohnmacht *et al.* 2006). Information about the indications, findings at surgery, and long-term outcomes for re-operations of different types of fundoplication is needed to better inform surgeons and patients about the associated risks and benefits of revisional surgery. Further, documentation of changes made to the antireflux barrier at revisional surgery that provide relief of troublesome dysphagia, may bring focus to technical elements requiring greater attention at primary surgery and may direct research for objective evaluation of these technical elements associated with dysphagia. This is the focus of a study in this thesis (Chapter 3).

A systematic review of re-operations has overcome to some degree, the problem of individual studies with small patient numbers (Furnee *et al.* 2009). In this review of 81 studies with findings for 4,509 patients, the most common indications for revisional surgery were identified as recurrent reflux (42%) and dysphagia (17%). In 5 studies, disruption of the hiatal repair and an overly tight fundoplication were more common with the laparoscopic than open approach (31.8% *vs.* 19.2%; 18.2% *vs.* 1.7% respectively). For patients undergoing re-operation for dysphagia, 15% had intra-thoracic wrap migration and 10% wrap disruption. The absence of a category for 'tight hiatal repair' was a glaring omission in this review, but perhaps it was not sufficiently reported to be included. While this report documented the type of primary surgery undertaken, the cause of failure was not stratified by operation type. The authors raised concern about the lack of standardised re-operative work-up given the unreliability of symptoms. In 43%

of patients undergoing revisional surgery for dysphagia, intra-operative inspection did not reveal any anatomical abnormality. The resounding message of these studies is that insights into the causes and thus best management of surgery-related dysphagia are woefully inadequate.

To date the procedures undertaken at revisional surgery for dysphagia are largely based on what is seen at re-operation. The strategy employed to facilitate intra-operative decision-making highlights the subjectivity inherent in this approach. An inspection of the anatomy is undertaken with a large oesophageal bougie (>52 Fr.) in place: if the hiatus is judged to be tight and the fundoplication loose, then the oesophageal hiatus is widened. If the hiatus is not tight, then the fundoplication is refashioned (even if it appears loose) (Watson *et al.* 1999a; Yau *et al.* 2000).

Endoscopic and fluoroscopic findings can help identify normal and abnormal features of antireflux surgery and assist with planning of revisional surgery (Raeside *et al.* 2012; Mittal *et al.* 2014). Both modalities however, predominantly identify anatomical abnormalities by careful review of the position of the OGJ, position of the fundoplication, status of the fundoplication (e.g. ± intact, twisted) and assessment of herniation. Endoscopic assessment has found that patients with a twisted fundoplication are more likely to present with dysphagia related to obstruction (Mittal *et al.* 2014). Anatomical abnormalities, such as a disrupted, twisted or slipped fundoplication and para-oesophageal herniation have been identified during endoscopy in up to 61% of patients presenting for revisional surgery for dysphagia. Yet endoscopy is of no diagnostic value for a large sub-group of patients (39%, 30/ 76) presenting for revisional surgery for troublesome dysphagia, who have an endoscopically normal-appearing fundoplication (Mittal *et al.* 2014).

1.8 AIMS

To date, the main strategy to reduce surgery-related dysphagia has been to vary aspects of surgical technique based on reasonable assumptions, but not actual data that are informative of the mechanical causes of this dysphagia. The overarching aims of this research were to devise strategies for reliable recognition of patients at risk of post-surgical dysphagia and to better define the mechanical factors that cause this problem. The studies of this thesis were undertaken to address the following specific aims:

1. To evaluate the mechanism of early post-operative dysphagia. It is often assumed that early post-operative dysphagia after laparoscopic fundoplication is due to oedema. Whether dysphagia is associated with a change in oesophageal motility and/or a change in oesophago-gastric junction characteristics of function is unknown.

2. To evaluate patients with late persistent dysphagia presenting for revisional surgery to ascertain the findings at surgery and the technical elements revised to treatment this symptom. To assess all patients presenting with symptoms warranting revisional surgery, to compare and contrast the indications for and symptomatic outcomes of late (>6 weeks) revisional surgery.

3. To explore factors that put a patient at risk of developing dysphagia after antireflux surgery.

4. To identify whether the mechanisms of early (<6 weeks) and late dysphagia ($\geq$ 6weeks) are the same or different.

5. To explore the relationship of pressures of oesophageal peristalsis to the movement of a swallowed bolus traversing the oesophagus with regard to dysphagia before and after antireflux surgery. This concept, conceived during the design phase of this course of study, underwent further conceptualisation and development of methods during the course of PhD candidature.

6. To explore, in greater detail than has occurred previously, the mechanics of the OGJ by measurement of radial pressure patterns along the length of the OGJ with regard to dysphagia after antireflux surgery.

2

Oesophageal Ileus Following Laparoscopic Fundoplication

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Name of Principal Author (Candidate)	Jennifer C Myers	
Contribution to the Paper	Co-designed and developed the study; Recruited subjects and performed the investigations; Analysed the physiological data, performed statistical analysis and interpretated the study findings. Drafted the manuscript including critical revision and submission for publication.	
Overall percentage (%)	85%	
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.	
Signature		Date 3, 2, 16

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i.   the candidate's stated contribution to the publication is accurate (as detailed above);

ii.   permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Glyn G Jamieson	
Contribution to the Paper	Conceived and designed the study. Supervised the development of the study; Performed or supervised antireflux surgery on study subjects; Contributed to critical revision and submission of the final manuscript.	
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Contribution to the Paper	Assisted with recruitment of patients for the study. Performed or supervised antireflux surgery on study subjects; Contributed to critical revision and approval of the final manuscript.
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DISEASES OF THE ESOPHAGUS

Original article

Esophageal ileus following laparoscopic fundoplication

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SUMMARY. **Early postoperative dysphagia occurs in most patients following laparoscopic fundoplication. Whether dysphagia is associated with a change in esophageal motor function and/or a change in gastroesophageal junction characteristics is unknown. Esophageal motility in the early postoperative period has not been evaluated previously. Esophageal motility was studied on the first postoperative day in 10 patients who underwent laparoscopic Nissen fundoplication and 10 patients who underwent laparoscopic cholecystectomy (control group), using standard perfusion manometry. Primary peristalsis on water swallows following fundoplication elicited a median response of 5% successful peristalsis compared with median response of 100% successful peristalsis following cholecystectomy ($P = 0.05$). The fundoplication was associated with failure of primary esophageal peristalsis in 7/10 patients, compared to 2/10 patients who underwent cholecystectomy ($P = 0.068$ Fisher's exact test). Three months after fundoplication, in nine patients studied, primary peristalsis was similar to peristalsis observed preoperatively in seven patients and two patients still had an aperistaltic esophagus. In this study, esophageal manometry 1 day after surgery demonstrated grossly disturbed esophageal motility in most patents following laparoscopic fundoplication, compared to normal motility following laparoscopic cholecystectomy. Peristalsis improved at 3 months or more following surgery. This suggests that an 'esophageal ileus' occurs during the early period after laparoscopic fundoplication.**

KEY WORDS: **dysphagia, fundoplication, gastroesophageal reflux, ileus, peristalsis.**

INTRODUCTION

Laparoscopic fundoplication is currently the most common approach to the surgical correction of pathological gastro-esophageal reflux. Unfortunately it is often followed by dysphagia, with several factors being implicated in its etiology.[1–3] Dysphagia is particularly common in the immediate postoperative period and most patients experience it to some extent, even following a partial fundoplication.[2,4] Several reasons for this problem have been postulated and these include: postoperative edema of the structures involved in the operation; technical errors in the fundoplication construction;[4] and the creation of a total fundoplication in the presence of abnormal esophageal motility.[1] Any or all of these factors might be important. However, esophageal motility and lower esophageal sphincter function might also be temporarily disturbed in the early postoperative period due to esophageal dissection and manipulation, and possibly muscle spasm of the esophagus or lower esophageal sphincter. Any disturbance in motor function would contribute to the problem of early postoperative dysphagia. To investigate this possibility, we performed esophageal manometry in the immediate period following laparoscopic fundoplication and compared the outcome with esophageal motility from a similar group of patients who underwent laparoscopic cholecystectomy.

PATIENTS AND METHODS

Patients

Patients referred for antireflux surgery were invited to participate in the study and recruitment then proceeded upon their agreement to participate. Twenty patients were recruited and the Human Ethics Committee of the Royal Adelaide Hospital

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approved the protocol for this study (ethics approval no. 970303).

Ten patients undergoing laparoscopic fundoplication formed one group (3 male, 7 female; mean age 51 years, range 22–78). Patients underwent a 360° Nissen fundoplication and are a subset from a larger cohort of patients in our department undergoing laparoscopic fundoplication. All of the patients had objectively proven gastro-esophageal reflux disease by either preoperative endoscopy and/or 24 h ambulatory pH monitoring. Esophageal manometry was undertaken as part of the routine preoperative assessment. Patients were excluded from consideration for this study if they had undergone a previous antireflux procedure or if they were on medications known to affect esophageal motility (e.g. anticholinergic agents, tricyclic antidepressants).

The other group consisted of 10 patients undergoing laparoscopic cholecystectomy (2 male, 8 female; mean age 55 years, range 27–78). These patients underwent a surgical procedure of similar duration to a fundoplication with similar anesthetic and operative conditions, but of course without intraoperative esophageal or gastric manipulation or dissection.

Surgical techniques and follow-up

Laparoscopic fundoplication was performed as described previously.[5] In brief, the hiatus was dissected, the hepatic branch of the vagus nerve preserved and the hiatus was repaired posteriorly with 1–3 nonabsorbable monofilament sutures. Short gastric vessels were not divided and a short, loose 360° fundoplication was secured over a 52 Fr bougie with three nonabsorbable sutures, with one suture including esophageal muscle.

Laparoscopic cholecystectomy was performed using a standard 4-port technique, using a combination of blunt dissection and electrocautery to dissect the cystic duct and artery. An operative cholangiogram was performed routinely, and the artery and duct were secured with metal clips.

The amount of peri-operative and postoperative anesthetic, analgesic and antiemetic agents was determined for the operation and the first 24 h postoperative period for each patient. The operative technique and duration of surgery were also recorded. For the fundoplication procedures, the number of sutures for hiatal repair and fundoplication, and the technique used for hiatal repair were also noted.

Each patient who underwent a fundoplication was interviewed peri-operatively, 3 months and 1 year after surgery by an independent investigator. Specific questions were asked to elicit information about dysphagia. A composite dysphagia score for nine food groups of increasing viscosity (e.g. water, milk, custard, jelly, eggs, fish, bread, apple, steak)

was recorded. Visual analog scales (VAS) determined difficulty with swallowing solid or liquid substances (0 = no difficulty swallowing, 10 = severe difficulty), with a score of more than 3 deemed in this study to indicate troublesome dysphagia.

Measurement of motility

At the end of surgery, an 8-channel esophageal motility catheter (lumina 0.74 mm; total 4.7 mm diameter) with an inner core (1.55 mm) (A-E1-LOSS-2, Dentsleeve Pty. Ltd, Adelaide, Australia) was introduced transnasally through the esophagus to the stomach by the anesthetist. The operating surgeon checked its position and it was secured with tape to the nose after a 50-cm length had been introduced. The catheter comprised of six proximal channels spaced 5 cm apart, a 6-cm sleeve sensor and one channel 4 cm distal to mid sleeve.

Twenty-four hours later, the catheter was connected to a mobile manometry recording unit which used a Denstleeve manometric perfusion pump similar to the hydraulic capillary infusion system described by Arndorfer *et al*.[6] The manometry catheter was connected to external transducers and perfused while data was acquired using dedicated computer software, Gastromac (v3.3.5.3 Neomedix Systems, Sydney Australia) as previously documented.[7]

Early postoperative manometry was performed at the bedside in the surgical ward. The fasting patient was positioned supine, and the pressure transducers were sited level with the patient's midcoronal plane. Prior to each study, the pressure transducers were water-perfused, electrically balanced and calibrated at the bedside. Before measuring esophageal motility, the lower esophageal sphincter or 'high pressure zone' was located by the station pull-through technique. The catheter was then positioned so the sleeve sensor was across the lower esophageal sphincter. Manometric measurements were recorded during two study phases: a 5-minute rest period and a series of 10 water-swallows. Water-swallows entailed the swallowing of a 5 mL bolus of water introduced through the mouth via a 10 mL syringe and each swallow was separated by a minimum of 20 seconds. At the end of the measurements the catheter was removed from the patient and standard postoperative care and dietary protocol was followed (free fluids and soft food diet).

Data analysis

The motility recordings were analyzed without knowledge of the symptom scores or operation details. The length of the high-pressure zone in the region of the fundoplication and the lower esophageal sphincter for cholecystectomy patients was determined by 1 cm withdrawal of the catheter

while recording pressure from a distal sidehole. The length of high-pressure zone was defined as the length (cm) from the level at which pressure rose above gastric end-expiratory basal pressure (> 2 mmHg) to the level at which pressure fell to esophageal end-expiratory basal pressure. Basal lower esophageal sphincter pressure (mmHg) was the resting pressure generated by the lower esophageal sphincter or high pressure zone and sampled during the 5-minute rest period (end expiratory pressure referenced to basal end expiratory intragastric pressure, median). Lower esophageal sphincter residual relaxation pressure (mmHg) was the lowest pressure (mmHg) that the sphincter relaxed to during water swallows (referenced to basal end expiratory intragastric pressure).

Peristalsis during primary swallows was regarded as 'successful' if the propagating pressure wave exceeded 10 mmHg pressure and the waves were non-synchronous, that is progressed distally along the esophagus. If the recordings in three or more of the esophageal body channels did not fit these criteria then peristalsis was deemed to be 'failure of primary peristalsis'. If all 10 water swallows showed failure of primary peristalsis then we referred to this as an aperistaltic esophagus. If the water swallows propagated the esophagus infrequently or with low contraction amplitude (< 40 mmHg) then we refereed to this as a hypoperistaltic esophagus. Measurements of contraction amplitude above the esophageal end-expiration baseline were determined by computer detection of wave peaks. The maximum pressure wave amplitude (measured in mmHg) for each swallow was determined separately in both the proximal and distal esophagus. Distal esophageal ramp pressures[8] were the measured pressure rise (mmHg) in the distal esophagus above baseline before the onset of the peristaltic contraction.

Patients who underwent a laparoscopic fundoplication also underwent esophageal manometry before surgery and 3 months following surgery, using a similar technique to that described above. Laparoscopic cholecystectomy patients were not investigated either preoperatively or at 3 months following surgery.

Statistical analysis

Data analysis was performed using a commercially available statistical analysis computer program (InStat version 2.01, GraphPad Software, San Diego, California). A two-tailed Mann-Whitney U-test was used to compare non-parametric data sets; Wilcoxon signed rank test was used for paired data sets. Fisher's exact or Chi-squared analysis was used for contingency tables. Statistical significance was accepted for P-values at $P = 0.05$.

RESULTS

During the study period, 26 patients met the study's inclusion criteria and provided written informed consent. In two patients, the attending anesthetist was unable to introduce the motility catheter into the stomach, and in two patients the catheter was dislodged from its position overnight before manometry could be performed. A further two patients' studies were not available for analysis because of computer problems (power failure; 'bad data blocks'). This left 20 patients in the study: 10 patients who underwent a fundoplication, and 10 a cholecystectomy. All fundoplications were successfully completed laparoscopically, whereas one cholecystectomy was converted to an open technique due to difficulty dissecting adhesions. Five patients undergoing fundoplication underwent repair of a concurrent sliding hiatus hernia. The hiatus was repaired posteriorly in seven patients, anteriorly in one, and with a combination of anterior and posterior sutures in two patients.

The median duration of surgery was 63 min (range, 35–90) for cholecystectomy and 68 min (range, 25–105) for fundoplication ($P = 0.3$, not significant). A similar quantity of narcotic analgesia (morphine or fentanyl) was utilized in the perioperative period in both surgical groups. Patients received an antiemetic: metoclopramide, droperidol, tropisetron or a combination. Metoclopramide was the antiemetic administered to most cholecystectomy patients (8/10 patients), while droperidol was administered to fundoplication patients (6/10).

All patients in the fundoplication group complained of some difficulty with swallowing on the first postoperative day, whereas no patients in the cholecystectomy group experienced dysphagia. Three months clinical and manometric follow-up was obtained for 9/10 patients who had undergone fundoplication, with one patient refusing further manometry. At 3 months, four patients had increased dysphagia for liquids and six increased dysphagia for solids (pre-op *vs.* post-op liquid dysphagia $P = 0.1$, solid dysphagia $P = 0.2$, not significant, Wilcoxon). Four of these patients had difficulty swallowing liquids and solids and two of these patients had an aperistaltic esophagus at day 1 and 3 months post-operatively. At 3 months there were four patients with no dysphagia for solids or liquids.

Esophageal motility on the first postoperative day: fundoplication compared with cholecystectomy

On the day after surgery, primary peristalsis on water-swallows following fundoplication elicited a median response of 5% successful peristalsis compared with median response of 100% successful peristalsis following cholecystectomy ($P = 0.05$).

Table 1 Motility characterictics recorded on the first post-operative day

Parameter	Cholecystectomy Day 1	Fundoplication Day 1	P-value
Primary peristalsis on 10 water-swallows (%)	100% (0–100)	5% (0–100)	$P = 0.05$
Patients with aperistaltic esophagus	1/10	5/10	
Patients with hypoperistaltic esophagus	1/10	2/10	
Patients with normal primary peristalsis	8/10	3/10	$P = 0.0698$†
LES resting pressure (mmHg)	7 (2–24)	21 (15–41)	$P = 0.002$
LES residual relaxation pressure (mmHg)	0 (0–5)	12.5 (7–23)	$P < 0.0001$
LES relaxation (%)	100 (71–100)	34.5 (0–71)	$P < 0.0001$
Length of HPZ (cm)	3 (1–4)	4 (3–7)	$P = 0.006$
Proximal peristaltic amplitude (mmHg)	43 (24–74)	50 (12–95)	$P = ns$
Distal peristaltic amplitude (mmHg)	134 (57–250)	47 (27–153)	$P = 0.006$

Data: median (range). Data analyzed for difference between medians of two unpaired datasets by Mann-Whitney U-test; †Fisher's exact test. $P > 0.05$ listed as ns (not significant). LES, lower esophageal sphincter; HPZ, high pressure zone.

Less than 70% of primary peristalsis in response to 10×5 mL water bolus occurred in 7/10 patients in the fundoplication group, compared to 2/10 patients in the cholecystectomy group ($P = 0.07$ Fisher's exact test). Seven of the fundoplication patients showed frequent or total failure of primary peristalsis and on this day all reported some difficulty with swallowing.

A completely aperistaltic esophagus on day 1 (Table 1) was the most common motility pattern observed in the fundoplication patients (5 patients), four were characterized by a contraction just below the upper esophageal sphincter then no contractions or peristalsis in the remaining esophagus. These findings contrasted with the completely normal primary peristalsis observed with each and every water-swallow recorded for 8/10 cholecystectomy patients (Fig. 1).

Further evidence of the contrasting peristaltic action in the two surgical groups was the significantly greater distal esophageal contraction amplitude of the cholecystectomy group compared to the fundoplication group (Table 1). Although only a

few of the fundoplication patients displayed any peristalsis on the day after surgery, peristaltic and non-peristaltic synchronous distal contractions were included for comparison of amplitudes.

Comparing lower esophageal sphincter function revealed a higher median resting pressure and incomplete relaxation of the lower esophageal sphincter on swallowing in the fundoplication patients compared with the cholecystectomy patients (Table 1). The manometrically determined length of the high-pressure zone (lower esophageal sphincter) was significantly longer in the fundoplication patients compared with the cholecystectomy patients (Table 1).

Fundoplication: esophageal motility at pre-, 1 day and 3 months postoperatively

Patients who underwent laparoscopic fundoplication had an esophageal manometry prior to surgery, with a median 90% normal propagation of peristalsis (Table 2) and distal peristaltic amplitudes ranging 18–83 mmHg above esophageal baseline. Median preoperative basal lower esophageal resting pressure was 4 mmHg (range, 0–15) and relaxation of the lower esophageal sphincter on swallowing was complete (0 mmHg).

A comparison of the preoperative and first day postoperative data showed there was a significant increase in lower esophageal sphincter pressure, and sphincter relaxation on swallowing was incomplete after surgery. The lower esophageal sphincter pressure characteristics recorded 3 months postoperatively were significantly greater than the preoperative measurements and less than the findings on the first postoperative day (Table 3).

There was no significant variation in the proximal and distal esophageal contraction amplitude of fundoplication patients between the preoperative period and 3 months after the operation. Three months after surgery, distal esophageal ramp pressures were commonly observed and were of significantly greater amplitude than preoperatively (Table 4).
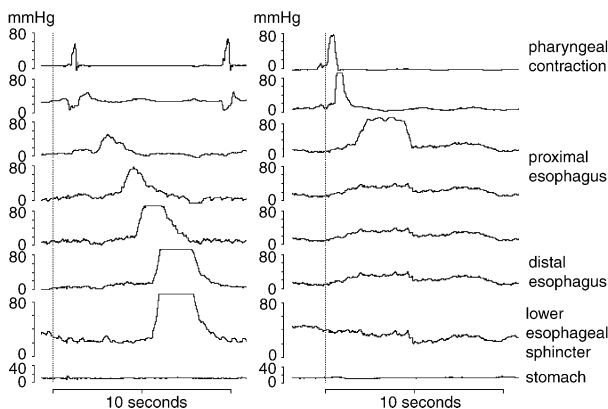

Fig. 1 Sample of esophageal motility recording 1 day after laparoscopic cholecystectomy (left) and fundoplication (right) (six proximal channels spaced 5-cm apart, a 6-cm sleeve sensor at the lower sphincter and one channel 4-cm distal to mid-sleeve).

Table 2   Fundoplication patients: esophageal peristalsis

Parameter	Before surgery	Day 1 after surgery	3 month after surgery
Primary peristalsis on 10 water-swallows (%)	90% (40–100)*	5% (0–100)*·**	60% (0–100)**
Patients with aperistaltic esophagus	0/10	5/10	2/9
Patients with hypoperistaltic esophagus	3/10	2/10	3/9
Patients with normal primary peristalsis	7/10	3/10	4/9

Data: median (range). Statistical comparisons: *$P = 0.02$; **$P = 0.06$ Wilcoxon signed rank test.

Table 3   Fundoplication patients: lower esophageal sphincter characteristics

Parameter	Before surgery	Day 1 after surgery	3 month after surgery
LES resting pressure (mmHg)	4 (0–15)*·**	21 (15–41)*·***	16 (14–26)**·***
LES residual relaxation pressure (mmHg)	0 (0–1)*·****	12.5 (7–23)*·**	8 (4–13)**·****
LES relaxation (%)	100 (93–100)*·****	34.5 (0–71)*·*****	50 (28–76)****·*****

Data: median (range). Statistical comparisons: *$P = 0.002$; **$P = 0.008$; ***$P = 0.05$; ****$P = 0.004$, *****$P = 0.04$ Wilcoxon signed rank test.

Table 4   Fundoplication patients: esophageal body motility

Parameter	Before surgery	Day 1 after surgery	3 month after surgery
Proximal amplitude (mmHg)	37 (13–77)	50 (12–95)	40 (16–50)
Distal amplitude (mmHg)	69 (18–83)	47 (27–153)	52 (25–86)
Ramp pressure (mmHg)	3 (0–7)*	–	18 (10–36)*

Data: median (range). Statistical comparisons: *$P = 0.006$ Mann–Whitney U-test; –, insufficient data for analysis.

Comparison of the pre- and first day postoperative findings in the fundoplication patients showed the percentage of successful swallows (primary peristalsis) recorded postoperatively was significantly less in seven patients and the same or similar in three patients ($P = 0.02$, Fig. 2). Nine of the fundoplication patients underwent esophageal manometry 3 months after the fundoplication. The number of propagated peristaltic water-swallows was similar to preoperative peristalsis in seven patients, while

Fig. 2 Percentage of swallows showing normal primary peristaltic waves (in response to 5 mL water-swallows). Horizontal bars = median.

two patients did not return to the preoperative pattern of peristalsis and were aperistaltic (Fig. 2). Interestingly the percentage of successful primary peristalsis at 3 months post-operatively inversely correlated with age (Spearman's rho = −0.92, $r^2 = 0.85$, $P = 0.0007$). The two aperistaltic patients were the oldest and third oldest patients of the group (78, 69 years).

Three months post-operatively, normal primary peristalsis was present in 4/9 patients (Table 2). In three patients peristalsis was present, but less than 70% of swallows successfully propagated the esophagus. Two of these patients had similar findings preoperatively. At day 1 postoperative manometry, five patients had an aperistaltic esophagus; this was sustained in two patients at 3 months post-operatively. Both of these patients had troublesome dysphagia during their postoperative hospital stay and at 3 months, reported severe dysphagia for both solids and liquids (visual analog solid score 10, 10; visual analog liquid score 10, 7). For one patient subsequent clinical follow-up revealed ongoing trouble with swallowing and at last assessment (18 months post-surgery) because of cure of his severe preoperative heartburn he reported feeling 'terrific', despite having a lot of trouble swallowing. Endoscopy found a mild to moderately dilated esophagus and a narrow lumen in the region of the wrap through which the endoscope
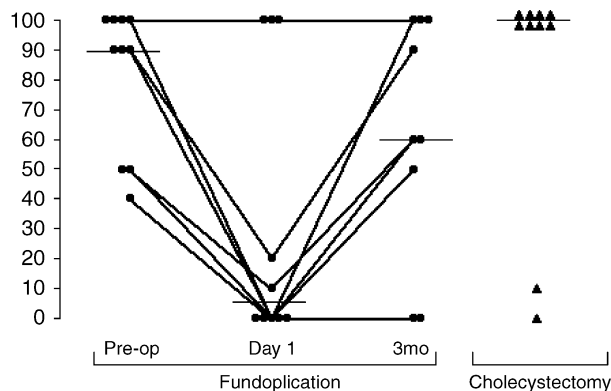
Table 5 Fundoplication patients: dysphagia scores

Parameter	Before surgery	3 month after surgery	1 year after surgery
Visual analog liquid score (0–10)	1.5 (0–5)	1 (0–10)**	0.5 (0–7)
Visual analog solid score (0–10)	2 (0–8)	6 (0–10)*·***	1.5 (0–7)*
Dysphagia 'nine-food types' score (0–45)	–	19 (0.5–32.5)**·***	12 (0–29)

Data: median (range). Statistical comparisons: Wilcoxon pairs signed-ranks test *$P = 0.027$; Spearman correlation **$P = 0.0005$, ***$P = 0.03$.

passed easily. An esophageal dilatation was undertaken with a 52Fr Savary Gillard dilator (18 mm) but made little difference to his swallowing. For the other patient, a clinical follow-up at 6 months post-surgery revealed he experienced a marked reduction of preoperative symptom of pharyngeal irritation and he had progressed from a diet of soft foods to being careful when eating red meat. A review of the two patients who remained aperistaltic at 3 months, showed one patient had a hypoperistaltic esophagus and mild dysphagia to solids prior to surgery, while the other had normal esophageal peristalsis and no dysphagia to solids. In both patients the lower sphincter pressure was 23 mmHg on day 1 post-operatively and 15 mmHg at 3 months

The visual analog scores for dysphagia were not statistically significantly different pre- and 3 months post-operatively (Table 5). The composite dysphagia score for nine food groups of increasing viscosity showed at 3 months that patients have trouble eating 42% of these foods. There was excellent agreement between the VAS and Composite Dysphagia Scores. Of the six patients with troublesome dysphagia at 3 months, four displayed significant loss of primary peristalsis one day after surgery but only two displayed an aperistaltic esophagus at 3 months post-surgery. There was a trend towards a linear relationship between increased Composite Dysphagia Score and increased distal esophageal ramp pressure ($P = 0.07$, $r^2 = 0.49$). Ramp pressure shows a trend in linear relationship to nadir pressure at 3 months post-operative manometry (Spearman's coefficient, $r^2 = 0.55$, $P = 0.06$).

Dysphagia scores at 1 year after surgery (Table 5) were significantly less for solids than 3-month scores (Wilcoxon signed rank test, $P = 0.027$) and similar to pre-operative solid dysphagia scores (Wilcoxon signed rank test, $P = 0.844$).

An evaluation of patients with regard to pre-existing hiatal hernia, revealed the incidence of pre-operative hiatal hernia was not associated with post-operative dysphagia or manometric abnormalities at day 1 and 3 months post-op testing (Fisher's exact test $P = 0.524$, $P = 1.00$, $P = 0.206$, respectively). All fundoplication patients underwent an hiatal repair, but there was no correlation between the number of stitches or type of hiatal repair and the incidence of dysphagia at 3 months post-operation.

DISCUSSION

The popularity of laparoscopic antireflux surgery heightens the need to understand adverse outcomes such as the problem of dysphagia following fundoplication. Most patients experience troublesome dysphagia in the early period following antireflux surgery and although most surgeons believe the incidence and severity of this problem in the immediate post-operative period is no different between laparoscopic and open surgery, reports occasionally appear suggesting the problem is more common following laparoscopic surgery.[9] There are several possible causes of early postoperative dysphagia[10] and the etiology of this problem is almost certainly multifactorial.

Technical problems such as the construction of a tight fundoplication, or tight esophageal hiatus when repairing the hiatal pillars can cause dysphagia.[11] These problems usually will not improve with conservative management and surgical re-intervention is often required.[11] The problem of a functionally tight fundoplication is of most importance in patients with gross esophageal motility disturbances, such as aperistalsis. However, any surgeon who has re-operated on such patients in the first few days after surgery knows that there is considerable tissue edema and induration of the dissected esophagogastric junction and fundoplication and this probably also contributes to dysphagia in the early post-operative period.

In addition to these factors, our study has demonstrated the occurrence of an esophageal ileus and we are not aware that this phenomenon has been reported previously. In most of the patients studied following fundoplication, esophageal motility was quite abnormal when assessed on the morning after surgery. Furthermore, in 70% of the fundoplication patients the pattern of esophageal peristalsis seen 3 months after surgery was similar to that observed pre-operatively. However, most striking was the abnormal motility in the fundoplication patients contrasting with the normal motility seen in the majority of patients in the laparoscopic cholecystectomy group, on the morning after surgery, even though both laparoscopic upper abdominal procedures were of similar duration.

The problem of a post-operative ileus affecting the motor function of the esophagus is perhaps not

surprising as the esophagogastric junction is extensively mobilized during laparoscopic fundoplication. It is well understood that manipulation of other parts of the gastrointestinal tract during open or laparoscopic surgery is followed by a transient loss of motility, that is, an 'ileus'.[12] The cause of the esophageal ileus we have identified is open to speculation. The ileus may be due to edema of the esophageal wall in the early post-operative period, although the edema should be confined to the lower-most 5–7 cm of the esophagus and the ileus affected a greater length of esophagus than this. It is also possible that dissection of the distal esophagus could disturb the intrinsic nerve supply to the esophageal wall, leading to a transient motility disturbance. A further possibility is that distal esophageal obstruction due to post-operative swelling has led to pseudo-achalasia and as the perihiatal edema subsequently improved the distal esophageal obstruction improved and esophageal motility recovered. However, the only animal study looking at the effect of esophageal obstruction on the development of aperistalsis, suggested this picture takes some time to develop with loss of peristalsis at 1 week and decreasing contraction amplitudes from 1 week through to 6 weeks.[13] A case study reporting two cases of stenosis of the cardia was associated with pseudo-achalasia-like motility (one developed in the short-term, the other long-term), which resolved to normal motility following surgical intervention.[14] The only other study we know of which looked at postoperative motility in the human esophagus very early after surgery was a study we undertook in patients having upper gastro-intestinal cancer surgery. We found the level of the anastomosis and the length of esophagus appeared to be related to the retained motility. With long lengths of esophagus retained, early peristaltic activity was evident but diminished over the first few post-operative days.[7]

Finally, the ileus could be due to medications given peri-operatively. It is well understood that certain classes of medication, in particular anesthetic agents, can affect esophageal peristalsis. However, narcotic analgesia (morphine and fentanyl) was utilized for laparoscopic fundoplication and cholecystectomy patients, yet primary peristalsis was retained in the latter group. The preferred antiemetic for the two surgical groups was different, metoclopramide following cholecystectomy, droperidol following fundoplication. The acute effects of metoclopramide include raised lower esophageal sphincter pressure with no effect on primary esophageal peristalsis.[15] The acute effects of droperidol on esophageal function are less clear. Studies to date suggest droperidol counteracts opioid-related inhibition of intestinal peristalsis and so, if anything, peristalsis should be enhanced by droperidol.[16,17]

Although this study has demonstrated disturbed motility on the first post-operative day, we did not study esophageal motility during subsequent days in the post-operative period and we therefore do not know when the ileus resolved. At 3 months post-operatively, the percentage of successful primary peristalsis inversely correlated with age. It is speculative to consider that older patients may take longer to regain their pre-operative motility pattern, for the numbers in this study were small. A long-term study to assess the time course of resolution is unlikely to be undertaken. Radionuclide liquid bolus transit has shown esophageal clearance to be disturbed at 3 days and 1 month post-operatively, and within normal range at 1 year post-operatively.[18] Although we did not obtain pre-operative manometry in the control (cholecystectomy) group, we think it is reasonable to assume that these patients had normal pre-operative esophageal motility, reflecting the usual range of esophageal motility in the community. None of the control patients had clinical gastro-esophageal reflux disease. It was of interest that two patients in the control group also had abnormal peristalsis when tested on the first postoperative day (2nd and 4th oldest, latter converted to open procedure for adhesions). However, all other patients had normal motility with 100% primary peristalsis and thus the two patients with disturbed motility do not influence the conclusions drawn from the overall results.

The raised lower esophageal sphincter pressure and residual relaxation pressure recorded the morning after and similarly 3 months after surgery are in keeping with documented findings following fundoplication.[4,8,19–22] Similarly, the occurrence of distal esophageal ramp pressure following fundoplication has been reported previously.[8,22]

At 3 months, the incidence of mild (2/10) to moderate/severe (4/10) dysphagia may seem high, but it should be remembered that this assessment was at 3 months post-operatively. We know from previously published work that whether short gastric vessels are divided, or not divided (as in these patients), showed no significant difference in dysphagia and beyond 12 months the rate of new onset dysphagia requiring dietary modification is less than 5%.[23] Furthermore, dysphagia decreased for both groups over time. The percentage of patients with dysphagia for lumpy solids was 56% at 1 month, ~50% at 3 months, ~30% at 6 months and ~30% at 5 years.[23,24] The incidence of dysphagia for solids in this study was 60% at 3 months, similar to previous findings.

At 1 year post-operatively, the dysphagia scores are lower than the 3-month scores and further support the temporary nature of troublesome dysphagia in the early post-operative period.

This study has demonstrated the occurrence of esophageal ileus during the first day following

laparoscopic antireflux surgery and this may contribute to the occurrence of dysphagia in the early period following laparoscopic antireflux surgery. This study cautions against patients resuming a normal diet immediately after antireflux surgery given the probability of reduced strength and co-ordination of peristaltic activity during this period.

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PUBLISHED ABSTRACT

Early findings of this study have been published in abstract form:
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3

LONG TERM OUTCOMES OF REVISIONAL SURGERY FOLLOWING FUNDOPLICATION

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Contribution to the Paper	Conceived and designed the study; Obtained and interrpreted operative notes and supporting documentation from medical records; Prospectively gathered patient re-operation data; Collated and analysed data, performed statistical analysis and interpretated the study findings. Co-drafted the manuscript including critical revision and submission for publication.
Overall percentage (%)	70%
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the second author of this paper.
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Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i.   the candidate's stated contribution to the publication is accurate (as detailed above);

ii.   permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Long-term outcomes of revisional surgery following laparoscopic fundoplication

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Background: A small proportion of patients who have laparoscopic antireflux procedures require revisional surgery. This study investigated long-term clinical outcomes.

Methods: Patients requiring late revisional surgery following laparoscopic fundoplication for gastro-oesophageal reflux were identified from a prospective database. Long-term outcomes were determined using a questionnaire evaluating symptom scores for heartburn, dysphagia and satisfaction.

Results: The database search found 109 patients, including 98 (5·6 per cent) of 1751 patients who had primary surgery in the authors' unit. Indications for surgical revision were dysphagia (52 patients), recurrent reflux (36), mechanical symptoms related to paraoesophageal herniation (16) and atypical symptoms (five). The median time to revision was 26 months. Outcome data were available for 104 patients (median follow-up 66 months) and satisfaction data for 102, 88 of whom were highly satisfied (62·7 per cent) or satisfied (23·5 per cent) with the outcome. Patients who had revision for dysphagia had a higher incidence of poorly controlled heartburn (20 *versus* 2 per cent; $P = 0·004$), troublesome dysphagia (16 *versus* 6 per cent; $P = 0·118$) and a lower satisfaction score ($P = 0·023$) than those with recurrent reflux or paraoesophageal herniation.

Conclusion: Revisional surgery following laparoscopic fundoplication can produce good long-term results, but revision for dysphagia has less satisfactory outcomes.

Introduction

Following the introduction of the laparoscopic approach, there has been a marked increase in the population-based rate of antireflux surgery[1]. Management of the small proportion of patients with recurrent symptoms or other problems is therefore of increasing importance. Despite specialist centres reporting success rates for laparoscopic fundoplication of 90–95 per cent[2], the true failure rate depends on the definitions used. Up to 50 per cent of patients may continue to use antireflux medication after fundoplication[3], even though only a minority of them have proven pathological reflux[4,5] and only 5–10 per cent ultimately require revisional surgery[6,7].

The most frequent reasons for needing surgical revision are recurrent heartburn and troublesome dysphagia, and such patients present a complex management problem. A number of recent studies have described the feasibility of laparoscopic revisional surgery and reported encouraging short-term outcomes[7–11]. However, there is a paucity of long-term clinical data to assist with counselling and management of these patients. The aim of this study was to evaluate long-term outcomes of revisional surgery following laparoscopic fundoplication for gastro-oesophageal reflux disease.

Methods

All patients requiring late revisional surgery who had undergone laparoscopic fundoplication for gastro-oesophageal reflux between October 1991 and December 2006 were identified from a prospective database. Patients who had the revision within 6 weeks of the original operation, those who had primary surgery for a large hiatus hernia (more than 50 per cent of the stomach in the

chest) and those who had open primary surgery were excluded. Analysis was confined to the patients' first revisional operation.

Revisional surgery was performed at the Royal Adelaide Hospital, Flinders Medical Centre or associated private hospitals by one of the unit's specialist upper gastrointestinal surgeons. Potential candidates underwent investigation for anatomical and physiological evidence of failure with a combination of upper gastrointestinal endoscopy, barium swallow, oesophageal manometry and 24-h pH studies.

Revisional surgery was offered routinely to patients with recurrent reflux symptoms not controlled by medical therapy, or when medical therapy was not tolerated. Reflux was confirmed by endoscopic evidence of oesophagitis or a positive 24-h pH study (pH less than 4 for more than 4 per cent of the study). Patients with significant persistent dysphagia were offered a trial of endoscopic dilatation before considering revisional surgery. The primary indication for revision was grouped as recurrent reflux, dysphagia, symptoms secondary to confirmed paraoesophageal herniation (chest or upper abdominal pain after eating, dyspnoea) or atypical symptoms. The latter group was not included in any subgroup analysis.

After 1995, laparoscopy was the standard operative approach for revisional surgery. Operative strategies were tailored to the specific clinical problem. Recurrent reflux was managed by re-exploration of the hiatal region. Adhesions were divided and the previous fundoplication was taken down. If present, a hiatal hernia was reduced and a crural repair performed. A 1–2-cm long, loose 360° wrap was routinely reconstructed over a 52-Fr intraoesophageal bougie, as described for primary antireflux surgery[12]. For patients undergoing revision for dysphagia, a flexible strategy was employed. After exposing the hiatus and dissecting between the oesophagus and anterior hiatus, a 52-Fr intraoesophageal bougie was passed beyond the gastro-oesophageal junction. The region was examined closely to determine whether the hiatus was tight or an anatomical abnormality of the wrap was present. If there was evidence of a tight hiatus, this was widened generously, usually by dividing the hiatal rim anteriorly or the left hiatal pillar anterolaterally. If there was any concern about the wrap, it was taken down and converted to a partial posterior or anterior fundoplication. Patients with symptoms from a paraoesophageal hernia underwent reduction of herniated structures with dissection of the hernia sac. A posterior crural repair, with or without anterior crural repair, was performed over a 52-Fr intraoesophageal bougie. Mesh or buttressed sutures were not used routinely. If the

fundoplication was known to be competent (no symptoms of recurrent reflux or objective evidence of reflux on preoperative investigation) it was left intact; otherwise it was refashioned.

Operative details and subsequent follow-up data were collected prospectively and stored in a database. Follow-up was conducted using a standardized structured questionnaire that evaluated symptom scores for heartburn, dysphagia for solids, and overall satisfaction with the outcome. This was administered by post or telephone by an independent non-clinical investigator 12 months after surgery and annually thereafter until December 2007, allowing a minimum of 12 months' follow-up. The presence or absence of heartburn and dysphagia for solids was graded using an analogue scale from 0 (no symptoms) to 10 (severe symptoms). A score of 7–10 was defined as poorly controlled symptoms. Patient satisfaction was also measured using an analogue scale from 0 to 10 (0–3, dissatisfied; 4–6, satisfied; 7–10, highly satisfied). The most recent follow-up data were included for each patient. For patients with at least 5 years' follow-up, a paired analysis of questionnaire outcomes at 1 and 5 years was performed. If data were incomplete, patient details were checked and further attempts were made to contact the patient by post and by telephone.

Statistical analysis

Statistical evaluation was performed using the SPSS® statistical package version 12 (SPSS, Chicago, Illinois, USA). Data are reported as mean (95 per cent confidence interval (c.i.)) or median (range). The χ^2 test was used to compare categorical data sets. Unpaired data were compared using the Mann–Whitney U test and Kruskal–Wallis test for multiple groups, and paired data were analysed using the Wilcoxon matched-pairs signed-ranks test. Statistical significance was accepted at $P < 0.050$.

Results

A total of 109 patients had late revisional surgery following laparoscopic fundoplication for gastro-oesophageal reflux disease in the authors' unit. There were 44 men and 65 women with a median age of 47 (range 19–78) years. The series included 98 of 1751 patients who had had primary surgery in the same unit during this time, giving a revision rate of 5·6 per cent. Eleven patients had undergone primary surgery at other institutions.

Table 1 Indications for revisional surgery in 109 patients

	No. of patients
Proven recurrent reflux	36 (33·0)
Endoscopic oesophagitis	23
Positive pH study	13
Dysphagia*	52 (47·7)
Mechanical symptoms of paraoesophageal herniation	16 (14·7)
Atypical symptoms†	5 (4·6)

Values in parentheses are percentages. *Thirty-two patients had a trial of endoscopic dilatation; five had already required early revision for dysphagia. †Gastric bypass for morbid obesity, delayed gastric emptying, gas-related symptoms, atypical chest pain, perforation at site of fundal sutures after consuming a carbonated drink[13].

Primary antireflux surgery

Primary antireflux surgery had been completed laparoscopically in all patients. The primary procedures were Nissen 360° fundoplication (83 patients), posterior 270° fundoplication (four), anterior 180° fundoplication (16) and anterior 90° fundoplication (six). At primary surgery, an intraoesophageal bougie was used to calibrate the hiatal repair and wrap, except in 15 patients undergoing anterior partial fundoplication. Sixteen patients who had the initial operation before 1994 did not have a hiatal repair, including six who developed a paraoesophageal hernia.

Revisional surgery

Table 1 shows the main indications for revision based on symptoms and preoperative investigations. The median time from primary antireflux surgery to revision was 26 (range 2–143) months. Seventy revisions (64·2 per cent) were performed within 3 years of the initial surgery. Eighty-nine revisional procedures (81·7 per cent) were undertaken laparoscopically, of which seven (8 per cent) were converted to

Table 2 Main operative findings and procedures performed at revisional surgery according to the indication

Main operative finding	Indication for revisional surgery			Operative procedure
	Reflux (*n* = 36)	Dysphagia (*n* = 52)	Paraoesophageal hernia (*n* = 16)	
Hiatal disruption	3		9	Hernia reduction and hiatal repair
	9		7	Hiatal repair and wrap revision
Anterior wrap (incompetent on preoperative investigations)	15			Conversion to 360° wrap
Tight hiatus		15*		Widening of hiatus†
		11		Widening of hiatus and conversion to partial wrap
Disrupted 360° wrap	4			Revision of 360° wrap
Slipped 360° wrap	2			Revision of 360° wrap
		1		Revision to a partial wrap
		1		Conversion to a partial wrap
Tight wrap		11		Conversion to a partial wrap
		1‡		Conversion of anterior to 360° wrap
No abnormality of 360° wrap/hiatus	3			Revision of 360° wrap
		11		Conversion to a partial wrap§
		1		Conversion to no wrap§

*Includes eight patients with dense hiatal fibrosis following 360° wrap. †Thoracoscopically in one patient. ‡Misplaced anterior fundoplication causing a bilobed stomach. §At patient's request.

Table 3 Analogue scores for heartburn, solid dysphagia and patient satisfaction according to indication for revisional surgery

	Indication for revisional surgery						
	Dysphagia	Reflux	Mechanical hernia	Reflux + hernia	Overall	*P*†	*P*‡
Heartburn score	3·1 (2·2, 4·0)	1·8 (1·1, 2·6)	1·4 (0·3, 2·4)	1·7 (1·1, 2·3)	2·4 (1·9, 3·0)	0·115	0·055
Dysphagia score	3·3 (2·5, 4·1)	2·3 (1·4, 3·3)	2·6 (1·2, 3·9)	2·4 (1·7, 3·2)	2·8 (2·3, 3·3)	0·331	0·154
Satisfaction score	6·4 (5·6, 7·2)	7·7 (6·8, 8·5)	7·7 (6·5, 8·9)	7·7 (7·0, 8·3)	7·0 (6·5, 7·5)*	0·076	0·023

Values are mean (95 per cent confidence interval). *The mean satisfaction score was lower for women (6·4 (5·7 to 7·2) *versus* 7·7 (7·0 to 8·4)) than for men (*P* = 0·021). †Dysphagia *versus* reflux *versus* mechanical hernia (Kruskal–Wallis test); ‡dysphagia *versus* reflux plus hernia (Mann–Whitney *U* test).
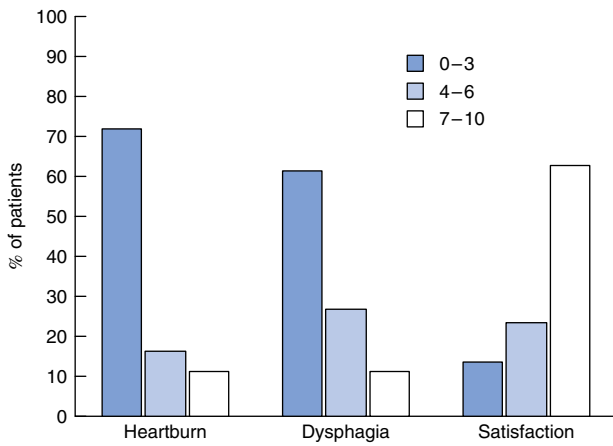
Fig. 1 Overall long-term outcomes of revisional antireflux surgery according to analogue symptom scores for heartburn and solid dysphagia in 104 patients, and satisfaction in 102 patients

Table 4 Comparison of analogue symptom scores at 1 and 5 years for 52 patients with at least 5 years' follow-up

	1 year	5 years	P*
Heartburn score	1·7 (1·1, 2·4)	2·2 (1·3, 3·1)	0·393
Dysphagia (solid) score	3·5 (2·6, 4·4)	2·7 (1·9, 3·5)	0·117
Satisfaction score	6·9 (6·1, 7·7)	7·0 (6·1, 7·8)	0·556

Values are mean (95 per cent confidence interval). *Wilcoxon test for two related samples.

open surgery. Nineteen patients had planned open revision (14 before 1995) and one was managed thoracoscopically.

Table 2 summarizes the main operative findings and revisional procedures, according to the indication for surgery. Twenty-one patients having revision for recurrent reflux had originally had a partial fundoplication (14 anterior 180°, five anterior 90° and two posterior 270°) compared with only three patients having revision for dysphagia (21 of 36 *versus* three of 52, $P < 0.001$). Twenty-six patients having revision for dysphagia had some degree of hiatal narrowing requiring widening, including eight patients with a rigid hiatus associated with dense fibrosis.

Fig. 2 Scores for **a** heartburn, **b** solid dysphagia and **c** satisfaction according to the indication for revisional surgery (recurrent reflux, dysphagia or symptoms of paraoesophageal herniation). *$P = 0.004$ *versus* reflux plus hernia for poor outcome (score 7–10); †$P = 0.118$ *versus* reflux plus hernia for poor outcome (score 7–10); ‡$P = 0.126$ *versus* reflux plus hernia for poor outcome (score 0–3)
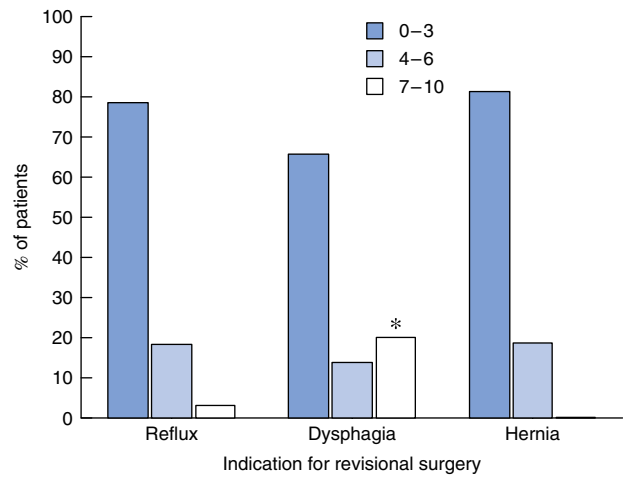
a Heartburn scores
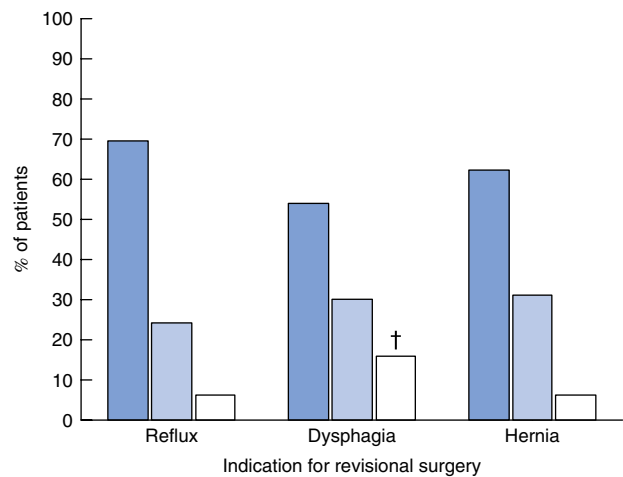
b Solid dysphagia scores
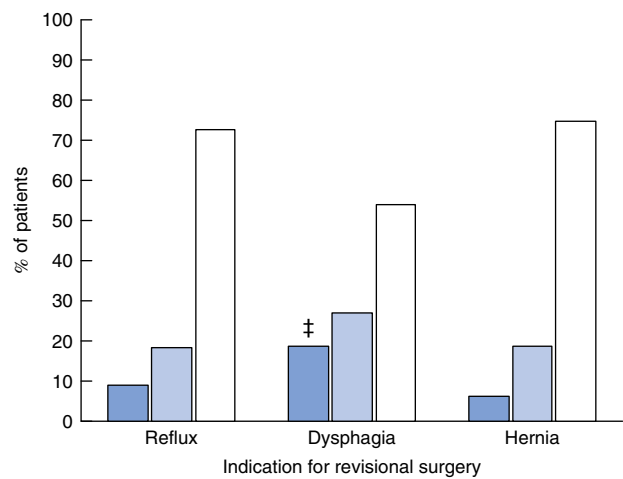
c Satisfaction scores

Gastric perforation occurred inadvertently in four procedures during dissection of the wrap. This was recognized at the time and repaired without further complication in all patients. Two patients required conversion to open surgery for bleeding, and five because the anatomy could not be defined safely. There were no deaths in hospital or within 30 days of revisional surgery.

Five patients (4·6 per cent) had further revisional antireflux surgery: one in the reflux group (to repair a paraoesophageal hernia), two in the dysphagia group (for conversion to a partial wrap after hiatus-widening surgery) and two in the group with symptoms suggestive of mechanical failure (for repair of further recurrence of a paraoesophageal hernia). The two patients treated for recurrent dysphagia remained symptomatic, whereas the three other patients were highly satisfied with the second revision. Two further patients underwent oesophagectomy for early adenocarcinoma of the lower oesophagus, 2 and 3 years after revisional surgery.

Outcome data were available for 104 (95·4 per cent) of 109 patients with a median follow-up of 66 (range 12–171) months. Data were unavailable for five patients who could not be contacted by telephone (four) or refused follow-up (one). Two further patients did not provide data on satisfaction. Follow-up symptom scores were available for 99 and satisfaction scores for 97 of 104 patients undergoing revisional surgery for reflux, dysphagia or mechanical symptoms.

Symptom scores and patient satisfaction at most recent follow-up are shown in *Fig. 1* and *Table 3*. Eighty-eight patients (86·3 per cent) were highly satisfied or satisfied with the outcome following revisional surgery. Scores at 1 and 5 years in 52 patients with at least 5 years of follow-up were similar (*Table 4*). Analysis of responses according to the indication for revision revealed that outcome in terms of heartburn, troublesome dysphagia and satisfaction was poorer for patients who had revision for dysphagia than for other indications (*Table 3*, *Fig. 2*).

The satisfaction score was similar whether an anatomical cause of dysphagia could be identified at the time of revisional surgery or not (mean 6·4 (95 per cent c.i. 5·5 to 7·3) *versus* 6·5 (95 per cent c.i. 4·4 to 8·6) respectively; $P = 0.831$). None of 15 patients reported poorly controlled heartburn after widening of a tight hiatus alone, compared with ten of 35 following other procedures to correct dysphagia ($P = 0.004$). Only one patient reported poor satisfaction after widening of a tight hiatus alone. Eight of 30 women undergoing revision for dysphagia reported poor satisfaction compared with one of 18 men ($P = 0.070$).

Discussion

Most patients in this series were satisfied with the long-term results of revisional surgery after laparoscopic fundoplication for gastro-oesophageal reflux, but the outcome was less satisfactory after revision for dysphagia.

Laparoscopic fundoplication is now an accepted treatment for gastro-oesophageal reflux, but its long-term efficacy is still being questioned[3,14]. Although most patients report good or excellent outcomes after 5 and 10 years[15,16], 5–10 per cent eventually undergo revisional surgery[7,17]. The revision rate was 5·6 per cent in the present study. There have been a number of encouraging reports of the short-term outcomes of revisional surgery[7,9–11], but follow-up was limited. These reports acknowledged the difficulty in obtaining detailed long-term outcome data, which are important in determining the overall role of laparoscopic fundoplication.

Validated symptom and patient satisfaction scores were used to obtain data for 104 (95·4 per cent) of 109 patients after a median of 66 months after revisional surgery. Some 86·3 per cent of patients were satisfied or highly satisfied with the outcome, and only five required a further surgical revision. These outcomes were maintained between 1 and 5 years, in keeping with short-term outcomes relating to patient satisfaction in other large studies[7,9,10]. When Iqbal and colleagues[18] used a ten-point scale to evaluate 104 patients at a median follow-up of 32 months, the mean satisfaction score of 7 was similar to that in the present study.

Although the overall results are encouraging, the proportion of patients with poorly controlled heartburn (11·5 per cent) or troublesome dysphagia (11·5 per cent) after revisional surgery was higher than the authors' rates after primary antireflux surgery at 5 years (4 and 4 per cent)[19] and 10 years (7 and 5 per cent)[15]. The mean satisfaction score (7·0) was also lower than those reported at 5 years (8·4) and 10 years (8·1) after primary surgery[16]. This is in keeping with previous findings that the success rate is lower for revisional surgery than primary surgery[7,10,20,21]. It was also noted that most of the patients were women, and that they reported lower satisfaction scores than men. Similar findings have been reported for primary antireflux surgery[22].

This study provides further support for the use of a laparoscopic approach for revisional antireflux surgery. There was a low incidence of intraoperative and postoperative complications, and no associated mortality. The incidence of intraoperative complications was lower than the 15–25 per cent reported previously[9,10,20]. This may be explained partly by the exclusion of patients who

had open primary surgery, who are recognized as a high-risk group[10].

Patients were classified according to the indication for revisional surgery as having recurrent gastro-oesophageal reflux, dysphagia, symptoms secondary to paraoesophageal herniation, or atypical symptoms. For patients with recurrent reflux due to hiatal breakdown or an incompetent partial fundoplication, repair of the hiatal defect or conversion to a floppy 360° fundoplication provided excellent results. Although not the primary focus of the study, it was noted that the pattern of failure appeared to be related to the type of original fundoplication. As reported previously[23], patients with a partial fundoplication were more likely to require revision for recurrent reflux than for other symptoms.

Although patients who underwent primary surgery for large paraoesophageal hernia were excluded from the study, 16 patients presented with a symptomatic paraoesophageal hernia. For six patients early in the series, this was probably because the hiatus had not been repaired formally at the time of primary surgery[24]. This group had a good outcome from a sutured hiatal repair. Two of 16 patients required further revisional surgery for recurrent herniation, similar to the symptomatic failure rate of primary surgery for large paraoesophageal hernia[25]. It has been proposed that the addition of a mesh cruroplasty may reduce the failure rate of revisional surgery[26]. This is being formally addressed in primary surgery by the International Society for Diseases of the Esophagus (Australasian Group) Large Hiatal Hernia Trial (Australian New Zealand Clinical Trials Registry number ACTRN12605000725662; http://www.anzctr.org.au).

A degree of hiatal narrowing requiring widening was identified in half of patients having revision for dysphagia, including eight patients with a rigid hiatus associated with dense fibrosis. This rare condition appears to be distinct from a hiatus sutured too tightly, although the aetiology is poorly understood[27]. Although the crucial role of the hiatus in postfundoplication dysphagia is recognized[28], the rate of hiatal narrowing in this study was higher than in some previous reports[18,29]. The reason is unclear as the hiatus had been calibrated with a bougie at the time of primary surgery in all but one patient. When a tight hiatus was clearly the only abnormality, leaving the wrap intact appeared to reduce the risk of developing troublesome reflux symptoms.

Although most patients undergoing revision for dysphagia reported good outcomes, there were higher rates of poorly controlled heartburn, troublesome dysphagia and poor satisfaction than in the other groups. Not only was dysphagia the most difficult symptom to improve[18]

but surgery, particularly conversion to a partial fundoplication, led to the development of reflux symptoms in some patients. Although a physiological abnormality was identified during preoperative investigation, no anatomical cause for dysphagia was identified at surgery for 12 patients. Perhaps surprisingly, although in keeping with results from another study[7], there was no difference in outcome between patients with and without an anatomical abnormality.

Suboptimal outcomes have been reported previously for patients with dysphagia[10,18,29], which has been identified as an independent risk factor for failure following revisional surgery[9]. This may reflect the inclusion of patients with underlying motility disorders and the difficulty of determining the true cause of dysphagia. Techniques such as high-definition oesophageal manometry with fluoroscopy[30] and multichannel intraluminal impedance[31] may aid selection for surgery and allow revision to be tailored to the precise cause of dysphagia.

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4

Dysphagia and Gastro-Oesophageal Junction Resistance to Flow Following Partial and Total Fundoplication

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iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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ORIGINAL ARTICLE

Dysphagia and Gastroesophageal Junction Resistance to Flow Following Partial and Total Fundoplication

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Abstract

Background Esophageal peristalsis and basal gastroesophageal junction (GEJ) pressure correlate poorly with dysphagia.
Aim To determine intraluminal pressures that reflect GEJ function and to determine manometric correlates for dysphagia before and after fundoplication.
Methods The relationships between maximal intrabolus pressure, residual GEJ relaxation pressure and peak peristaltic pressure for water swallows were determined in normal volunteers and patients with reflux disease before and after fundoplication. GEJ anatomy was assessed by radiological, endoscopic and surgical criteria, whilst dysphagia was measured with a validated composite dysphagia score.
Results Dysphagia was significantly associated with lower peak peristaltic pressure in the distal esophagus and the presence of a hiatus hernia preoperatively, as well as higher residual pressure on GEJ relaxation postoperatively. Peak distal peristaltic pressure and residual GEJ relaxation pressure were predictors of intrabolus pressure after total fundoplication ($p<0.002$). Residual GEJ relaxation pressure was four times higher after 360° fundoplication ($N=19$) compared to 90° fundoplication ($N=14$, $p<0.0001$). Similarly, intrabolus pressure was elevated 2.5 times after 360° fundoplication and nearly doubled after 90° fundoplication and both were significantly different from controls ($N=22$) and reflux disease patients ($N=53$, $p<0.0001$).
Conclusions Gastroesophageal junction impedance to flow imposed by fundoplication is associated with dysphagia when there is suboptimal distal esophageal contraction strength and relatively high residual GEJ relaxation pressure.

Keywords Gastroesophageal junction · Manometry · Dysphagia · Reflux disease · Hiatus hernia · Laparoscopic fundoplication

Abbreviations
GEJ Gastroesophageal junction

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Introduction

Laparoscopic fundoplication has a well-proven antireflux effect, but outcomes are sometimes marred by postoperative dysphagia, gas bloat and an inability to belch.[1,2] These side effects are either the result of restricted GEJ movement or altered gastrointestinal tract function secondary to fundoplication. Fundoplication certainly imposes a restriction to GEJ opening, resulting in an impedance to flow that is not normally present[3] and this restriction remains during swallowing and transient sphincter relaxations.[4]

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Objective measurements of GEJ function hold the key to better understanding of the mechanics of antireflux procedures and for minimising adverse outcomes. GEJ relaxation during swallowing and transient sphincter relaxations has two components: relaxation of the intrinsic or lower esophageal sphincter and focal inhibition of the diaphragmatic crura during inspiration. Normally, these relaxations significantly reduce intraluminal pressure within the GEJ and frequently abolish it completely. The pattern of GEJ relaxation is often altered by antireflux surgery, rendering it incomplete. This incomplete GEJ relaxation, which can be detected by manometry, reflects impedance to flow at the GEJ and has been linked with dysphagia after fundoplication.[5] Another objective measure, intrabolus pressure, is generated when a swallowed bolus is compressed between the driving force of the oncoming peristaltic esophageal contraction against the pressure generated by the GEJ (Fig. 1).[6,7] Thus, intrabolus pressure reflects both GEJ and esophageal body function. Intrabolus pressure is most pronounced in the distal esophagus and is greatly increased by esophageal outflow restriction in experimental animals and during elevation of intragastric pressure by abdominal compression in humans.[6–8] In the clinical setting, total fundoplication and possibly hiatal hernia alter intrabolus pressure.[5,9]

Dysphagia is an intriguing symptom that is experienced prior to surgery by some patients with reflux disease in the

absence of stricture and also by some patients after surgery. The physiology of both preoperative and postoperative dysphagia is poorly understood. Objective physiological studies with formal assessment of dysphagia are rarely conducted both pre- and postoperatively, because these studies require a high level of commitment by the patient and investigator. So although substantial data support the relevance of intrabolus pressure and the extent of GEJ relaxation as useful indicators of GEJ mechanics, there remains a lack of understanding of how dysphagia relates to these manometric measures.

To address this knowledge gap, we undertook this prospective study using standardised methods to evaluate dysphagia, intrabolus and residual GEJ relaxation pressures in normal volunteers, patients with reflux disease with and without hiatal hernia, and in a subgroup of patients before and 5 months after partial and total fundoplication.

Methods

Study Overview

Patients referred for esophageal function tests as part of a preoperative assessment were invited to participate. Patients who underwent fundoplication were reevaluated 5 months after surgery. Subjects were excluded if they had a primary motility disorder such as scleroderma and achalasia, atypical reflux symptoms, a large hiatus hernia (>5 cm) or previous antireflux surgery. Healthy age-matched control subjects were recruited from responses to advertisement in community newspapers (those experiencing heartburn or regurgitation at least weekly were excluded). Written informed consent was obtained from all subjects and the Human Research Ethics Committee of the Royal Adelaide Hospital approved the protocol.

Age, gender and body mass index were systematically recorded. Subjects completed a self-administered questionnaire to evaluate heartburn, regurgitation and dysphagia using visual analogue scales (VAS, 0–10 scale, 10=severe). A validated dysphagia composite score recorded difficulty with swallowing a range of foods of increasing viscosity (scale 0–45).[10] Abnormal 24 h distal esophageal acid exposure (≥4% time pH<4), endoscopically evident erosive or ulcerative esophagitis[11] or Barrett's esophagus with intestinal metaplasia were considered proof of reflux disease. The presence, type and size of a hiatus hernia were noted from endoscopy and barium swallow[12] reports obtained from referring specialists. In addition, the primary surgeon categorised the size of hiatus hernia seen at operation as small (<2 cm), medium (2–5 cm) or large (>5 cm). Postoperatively, patients recorded their satisfaction with surgical outcome using a visual analogue scale (0–10).
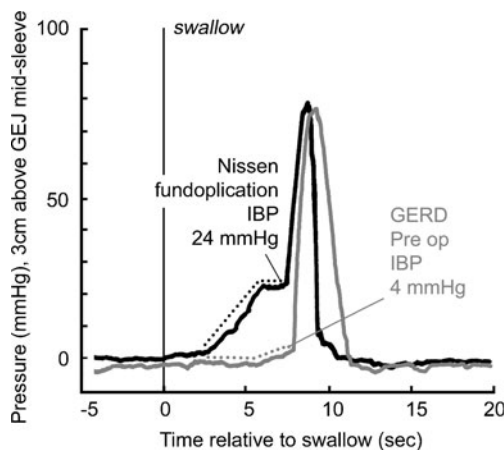

Fig. 1 Distal esophageal intrabolus pressure (IBP) during esophageal peristalsis in the same individual before and after 360° fundoplication. Intrabolus (or distal esophageal ramp) pressure appears as a steadily increasing pressure rise (ramp) with a plateau, which precedes the upstroke of pressure generated by the esophageal peristaltic contraction.[34–36] The plateau itself occurs as the esophagus dilates to accommodate the compressed bolus as it is propelled distally by advancing peristalsis.[34] The plateau of the intrabolus pressure ends when the pressure in the bolus and the peristaltic contraction equals or exceeds the pressure within the GEJ (exceeds residual GEJ relaxation pressure).[6,37,38] The dynamic change in intraluminal pressure just above and within the GEJ is accompanied by relaxation and opening of the GEJ, a drop in pressure in the direction of flow occurs and the bolus flows into the stomach[6,37,38]

Manometric Technique

Esophageal manometry was performed using a water perfused manometric catheter with a 6 cm sleeve (3.5 mm diameter Dentsleeve International, Mississauga, Canada), which was introduced transnasally to the stomach. The catheter was taped into position so the sleeve was across the GEJ, with six proximal side holes spaced 5 cm apart and a distal side hole for intragastric pressure. The manometric recording system digitised pressures at 40 Hz (Gastromac v3.3.5.3, Neomedix Systems, Sydney Australia).

H_2 receptor antagonists were withheld for 48 h and proton pump inhibitors were ceased 5 days prior to testing. After a 6-hour fast, subjects underwent manometry using a standard protocol (supine, 5-min rest period then ten 5-mL water swallows, each 30 s apart).

Data Analysis

Esophageal primary peristaltic success was recorded as the percentage of complete peristaltic sequences (esophageal peak pressure ≥10 mmHg above esophageal end-expiration baseline for at least four of five esophageal channels). The median basal end-expiratory GEJ pressure referenced to end-expiratory intragastric pressure was recorded from the rest period. GEJ length was determined as the distance between the level (cm) at which pressure rose above gastric pressure (≥2 mmHg) to GEJ lumen pressure and the level when pressure fell (≥2 mmHg) to esophageal basal pressure.

The following end-expiratory pressures were measured for each *individual successful* water swallow: distal esophageal peristaltic pressure (8 cm and 3 cm above the GEJ, mmHg); maximal intrabolus pressure prior to the peristaltic pressure wave upstroke (3 cm above the midpoint of GEJ, mmHg); residual GEJ (nadir) pressure as a result of swallow induced GEJ relaxation (residual GEJ relaxation pressure, mmHg); and basal GEJ pressure within 5 s prior to swallow initiation (mmHg). Failed swallows (contraction peak pressure ≤10 mmHg for two or more adjacent esophageal channels); swallows with synchronous esophageal pressure waves and double swallows were excluded, because without successful peristalsis there is insufficient force to compress the bolus against GEJ pressure.

Laparoscopic Fundoplication

Patients with proven reflux disease who were suitably fit were offered laparoscopic fundoplication. The type of fundoplication undertaken was determined by informed patient preference. For total fundoplication, a loose 2-cm long 360° wrap was constructed over a 52Fr intraesophageal bougie, without division of the short gastric vessels.[13]

A partial fundoplication included a posterior esophagopexy to the right hiatal pillar, fixation of a length of esophagus within the abdomen, recreation of the angle of His, and construction of an anterior 90° fundoplication that covered the left anterolateral intraabdominal esophagus.[13,14] In both procedures, the esophageal hiatus was routinely repaired with posterior sutures.

Statistical Methods

Data analysis was performed on both a per individual swallow and per subject basis.

Subject Analysis Normally distributed data (mean ± SEM) were compared between groups using independent samples *t*-tests and one-way ANOVA models, whilst continuous data that were not normally distributed (median, interquartile range IQR {Q1–Q3}) were compared using Mann–Whitney and Kruskal–Wallis tests. Fisher exact tests were used to analyse simple contingency tables. Paired pre- and post-fundoplication data were analysed using a Wilcoxon signed rank tests for continuous data and McNemar tests for proportions. Predictors of the presence of dysphagia amongst patients were assessed using logistic regression models.

Individual Swallow Analysis Intraluminal pressures were analysed using linear mixed effects models. Patient identity number was entered as a random effect to adjust for dependence due to a subject being in more than one group (pre- and postsurgery) and for multiple swallows (ten swallows per subject). Where required, outcome data were log transformed prior to analysis, and then back-transformed to give estimates on the original scale (median value). Linear mixed effects were used to compare intraluminal pressures across groups (healthy controls, reflux patients ± hiatus hernia and patients for two types of fundoplication) and to identify predictors of intrabolus pressure.

All statistical calculations were performed using Instat (version 3.0b, GraphPad Software Inc., San Diego, California) and SAS (version 9.2, SAS Institute Inc., Cary NC, USA). Significance was accepted for *p* values less than 0.05.

Results

Study Population

Twenty-five healthy control subjects met entry criteria; however, three were excluded because cardiac compression obscured intrabolus pressure. Of 65 patients with suspected reflux disease, 12 patients were excluded because of large

hiatus hernia (n=2), poor esophageal motility (n=2; <50% primary peristalsis) or lack of proof of reflux disease (n=8). Patients with reflux disease were divided into those with a hiatus hernia (reflux HH, n=24) and those without (reflux noHH, n=29). Erosive or ulcerative esophagitis was found in 30 patients and Barrett's esophagus in nine patients.

From the above group of 53 patients with reflux disease, antireflux surgery was the preferred treatment for 33 patients, whilst 20 patients chose continuation of medical therapy with an option for further review if required. Fundoplication was either a partial 90° anterior fundoplication (14 patients) or total 360° fundoplication (19 patients). Female patients tended to prefer a partial fundoplication, whilst many males chose a total fundoplication (Table 1). Prior to surgery, 17 of 33 patients had a sliding hiatus hernia <5 cm in size with operative confirmation in 13 patients (76% concordance).

Surgery significantly reduced reflux symptoms in all patients. After total fundoplication, more patients were free of reflux symptoms compared with partial fundoplication (89% cf. 50% heartburn free and 75% cf. 43% regurgitation free, respectively) and were slightly more satisfied with their surgery (median VAS 10.0{9–10} vs. 8.5{7–9}, respectively p=0.05).

Prevalence of Dysphagia

The prevalence of dysphagia in patients with reflux disease, as well as patients before and after fundoplication is shown in Table 2. Five months after fundoplication, no patient experienced severe dysphagia (VAS score>7/10). New onset dysphagia was reported after total and partial fundoplication (9/19 patients vs. 2/14 patients, respectively, p=0.06) (Fig. 2), with a small but significant increase in severity of dysphagia following total fundoplication (Table 2).

Measures of GEJ Compliance

Residual Pressure during Swallow Induced GEJ Relaxation Both types of fundoplication significantly raised residual GEJ relaxation pressure; however, the pressure elevation was four times higher after 360° fundoplication compared to 90° fundoplication (Table 3; Fig. 3).

Intrabolus Pressure Following 90° fundoplication, intrabolus pressure nearly doubled and more than doubled (about 2.5 times) in 360° fundoplication patients (Table 3). For the 360° fundoplication group, 95% of patients had an intrabolus pressure less than 15 mmHg preoperatively and greater than 15 mmHg postoperatively (Fig. 3).

Resting Gastroesophageal Junction Pressure Table 3 shows that, compared with controls, GEJ resting pressure was significantly lower in reflux disease patients and significantly elevated following 360° fundoplication but not following 90° fundoplication (Table 3).

Length of Gastroesophageal Junction Pressure The manometric length of the GEJ increased after 360° fundoplication (median{IQR} 2{2–3} cm, vs. 4 {3–4} cm, p=0.03), but not significantly after 90° fundoplication (3{2–3.8} cm vs. 3.5{3–4} cm, p=0.19, pre- op vs. postop respectively).

Relationships Amongst Intraluminal Pressures

In all groups there was a positive correlation amongst distal esophageal peak pressure, GEJ resting pressure, residual GEJ relaxation pressure and intrabolus pressure (Fig. 4, reflux disease patients not shown). Distal esophageal

Table 1 Demographic data

	Healthy control N=22	Patients with reflux disease N=53	P value	Fundoplication anterior 90° N=14	Fundoplication Nissen 360° N=19	P value
Age[a], years	43 (24–74)	47 (18–77)	0.26[c]	54 (31–78)	47 (25–71)	0.06[c]
Gender, M: F	10: 12	28: 25	0.06[d]	2: 12	17: 2	**<0.0001[d]**
BMI[b], kg/m²	24.9±0.8	28.8±0.7	**0.001[c]**	25.4±1.3	28.9±0.8	**0.02[c]**
BMI <25	12	9		8	1	
25–29	7	21		3	9	
30–34	3	16		2	9	
≥35	0	7		1	0	
Height[b], cm	170.6±2.6	170.4±1.4	0.93[c]	163.7±1.9	174.8±1.8	**0.0003[c]**

[a] Data are mean (range)

[b] Data are mean (±SEM)

[c] Independent t-test

[d] Fishers's exact test

Significant differences shown in bold type

Table 2 Prevalence of dysphagia

Group	N	Dysphagia = Yes	Dysphagia for solids only	Dysphagia for liquids score (0–10)	Dysphagia for solids score (0–10)	Composite dysphagia score (0–45)
Patients with reflux disease	53	22 (42%)	11 (21%)	0 {0–0}	0 {0–2}	0 {0–12}
Subset of reflux patients prior to fundoplication	33	12 (36%)	7 (21%)	0 {0–0}	0 {0–2}	0 {0–5}
90° fundoplication						
Preop	14	8 (57%)	4 (29%)	0 {0–1}	0 {0–4}	3 {0–15}
Postop	14	10 (71%)	4 (29%)	0 {0–1}	0 {0–3}	4 {0–13}
360° fundoplication						
Preop	19	4 (21%)*	3 (16%)	0 {0–0}	0 {0–0}	0 {0–0}[†]
Postop	19	13 (68%)*	7 (37%)	0 {0–1}	1 {0–2}	4 {0–12}[†]

Data are number (%) or median {IQR}

*$p=0.003$ McNemar test

[†] $p=0.02$ Wilcoxon matched-pairs signed-ranks test

peristaltic pressure was found to be a predictor of intrabolus pressure in all groups except the 90° fundoplication group. For example, in control subjects for every 1 mmHg increase in distal esophageal peak pressure, there was an estimated 0.03 mmHg increase in intrabolus pressure (Table 4).

Following 360° fundoplication, residual GEJ relaxation pressure was a predictor of intrabolus pressure in addition to distal esophageal peak pressure so that for every 1 mmHg increase in residual GEJ relaxation pressure, there was an estimated 0.3 mmHg increase in intrabolus pressure and for every 1 mmHg increase in distal esophageal peak pressure, there was an estimated 0.04 mmHg increase in intrabolus pressure.

Association of Gastroesophageal Junction Anatomy and Function with Dysphagia

Dysphagia in Patients with Reflux Disease In patients with reflux disease, greater distal esophageal peak pressure was

Fig. 2 Dysphagia for solids score before and after fundoplication (*horizontal bar* is mean value)

associated with a reduced likelihood of dysphagia (odds ratio=0.97, 95% CI 0.95–1.00, $p=0.02$). Reflux HH patients were far more likely to experience dysphagia than reflux noHH patients (odds ratio=0.27, 95% CI 0.09–0.86, $p=0.03$). These reflux HH patients were also significantly older than reflux noHH patients (52.9 {27–77} years vs. 42.8 {18–69} years, $p<0.01$) and experienced significantly greater regurgitation (median score 7.5 {5–10} vs. 5{3–8}, respectively, $p=0.01$).

Dysphagia after Fundoplication After partial fundoplication, greater distal esophageal peak pressure was associated with a reduced likelihood of dysphagia (odds ratio=0.94, 95% CI 0.89–1.00, $p=0.049$), but this finding was not significant for total fundoplication ($p=0.36$).

To further interpret manometric data in the light of pre- and postoperative dysphagia, data for both types of fundoplication were pooled and patients were grouped according to their pattern of dysphagia. There were four groups, patients with (1) no dysphagia pre- or 5 months postoperatively; (2) dysphagia before and after fundoplication; (3) dysphagia postop only and (4) dysphagia preop only. Analysis of intraluminal pressures by dysphagia status (Table 5) showed patients with 'post operative dysphagia only' had higher mean postoperative residual GEJ relaxation pressure. Patients with 'no dysphagia pre or postoperatively' had higher mean postoperative distal esophageal peak pressure than patients with dysphagia before and after surgery. Patients with new onset postop dysphagia had significantly greater increase in residual GEJ relaxation pressure than patients with dysphagia before and after surgery (7.4±1.7 mmHg *cf.* 2.5±0.5 mmHg, $p=0.046$). Postoperative residual GEJ relaxation pressure correlated with increased dysphagia for solids after fundoplication (linear regression $r^2=0.17$, $p=0.02$).
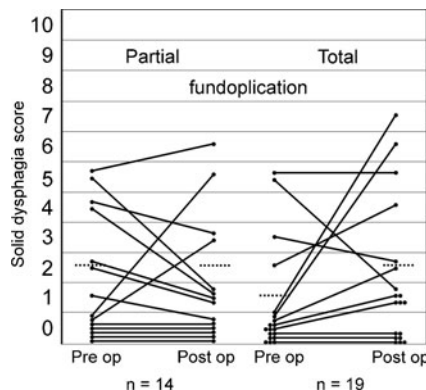
Table 3 Distal esophagus and gastroesophageal junction pressures

Pressures with water swallows[a]	Healthy controls N=22	Reflux patients, no hiatus hernia N=29	Reflux patients, with hiatus hernia N=24	Fundoplication anterior 90° N=14	Fundoplication Nissen 360° N=19	P value
Esophageal peak pressure 8 cm above GEJ, mmHg	90.1±8.1	72.1±6.2	71.1±6.9	68.6±9.4	77.5±8.3	0.33
Intrabolus pressure, mmHg	9.6±0.7	9.9±0.6	8.4±0.7	15.1±1.6[†]	23.5±1.3[†]	**<0.0001**
GEJ basal pressure immediately prior to swallow, mmHg	17.4±1.4[§]	10.1±1.3[§]	7.3±1.3[§]	16.8±2.5[§]	26.0±2.1[§]	**<0.0001**
Residual GEJ relaxation pressure, mmHg[b]	0.7	0.4	0.3	1.5[*]	6.0[*]	**<0.0001**
Pressures recorded during rest						
GEJ basal pressure during rest period, mmHg	18.3±1.7[O]	7.9±1.4[O]	5.5±1.6[O]	13.2±2.0[O]	25.7±1.7[O]	**<0.0001**

Data are mean (±SEM). *GEJ*, gastroesophageal junction

Analysed using linear mixed effects model, *P* values were adjusted for multiple comparisons using the step-down Sidak method:

[†] $p < 0.006$ compared with all other groups

[§] $p < 0.01$ compared with all other groups, except: Reflux, HH were not significantly different from Reflux, noHH; 90° fundoplication were not significantly different from healthy controls

[*] $p < 0.004$ compared with all other groups

[O] $p < 0.02$ compared with all other groups, except: Reflux, HH were not significantly different from Reflux, noHH; 90° fundolication were not significantly different from Reflux, no HH and healthy controls

[a] Parameters determined for individual water swallows

[b] Data are right skewed, log transformed, analysed using linear mixed effects model (data are median)

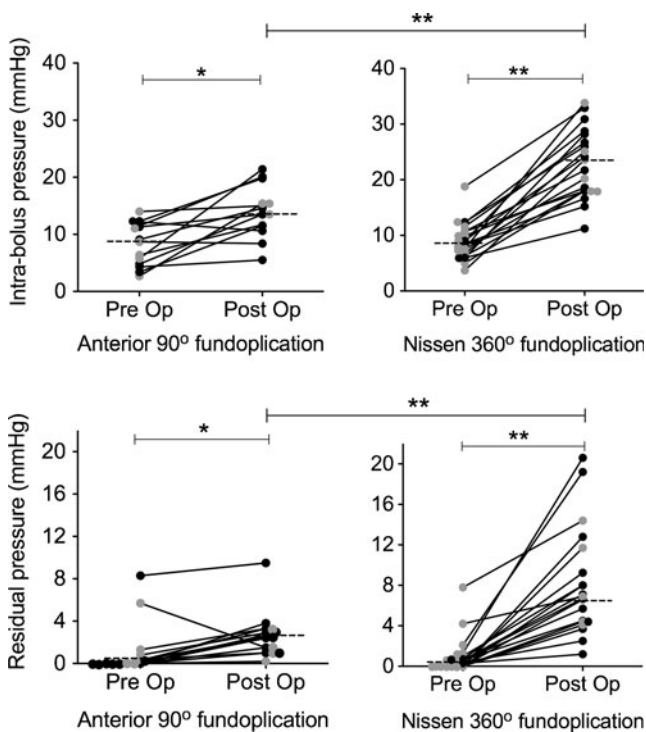Significant differences shown in bold type

Fig. 3 Fundoplication significantly altered intrabolus pressure and residual GEJ relaxation pressure, with greater change after total fundoplication (n=19) than partial fundoplication (n=14) (*p≤0.01, **p<0.0001). *Median bar*. Dysphagia status is shown as *black dot* dysphagia; *gray dot*, no dysphagia

Discussion

The major novel findings of this study are that dysphagia is linked with both suboptimal esophageal driving pressure pre- and postoperatively and the degree to which GEJ compliance is reduced by fundoplication. These findings are what we might expect intuitively and yet neither we,[5,15] nor others[16,17] have used a systematic approach to demonstrate these relationships.

Our study highlights that postfundoplication dysphagia is related to two things. First is the resistance to flow at the GEJ imposed by fundoplication. We found that a large increase in residual GEJ relaxation pressure was associated with *new onset* postop dysphagia. Further, we found that the circumferential extent of the fundal wrap significantly influenced intrabolus pressure and residual GEJ relaxation pressure. Many previous studies have concentrated on findings for one type of operation such as total fundoplication[5,18,19] or inappropriately focused on GEJ resting pressure. GEJ relaxation can only be reliably recorded with a sleeve or with pressure sensors spaced at no more than 1 cm intervals.[20] Anderson et al.[15] and Engstrom et al.[16] used a catheter with a sleeve and also found these intraluminal pressures were elevated in proportion to the extent of fundoplication. However, these studies did not evaluate

patients preoperatively and postoperative findings were not interpreted in the light of preoperative dysphagia. In the present study, dysphagia was significantly associated with higher residual pressure on GEJ relaxation postoperatively.

Second, our study shows that dysphagia is related to suboptimal esophageal contractile strength. Preoperatively, patients with reflux disease and low distal esophageal contraction pressure were more likely to experience dysphagia. Patients who did not report dysphagia before or 5 months after surgery had significantly higher distal esophageal contraction pressure. Furthermore, distal esophageal peak pressure was a predictor of intrabolus pressure in all groups except following anterior 90° fundoplication, which is possibly a type II statistical error due to the small number of subjects in this group. Similarly, residual GEJ relaxation pressure was also a predictor of intrabolus pressure, although less consistently. This suggests that residual GEJ relaxation pressure during swallowing produces resistance to flow through the GEJ so that higher intrabolus pressure is required for flow to occur. A stronger distal esophageal contraction will generate greater bolus compression against the less compliant GEJ, evident as higher intrabolus pressure.

We propose that the esophagus adapts to increased GEJ resistance to flow by generating higher esophageal contraction pressures and that limits in this adaptive response may result in impaired bolus transit,[6,19] and dysphagia.[21] Scheffer et al.[18] have proposed that greater esophageal contraction strength is necessary to overcome increased GEJ resistance after fundoplication. Our study takes this concept one step further, as our findings suggest that, independent of fundoplication, there is an inherent adaptive esophageal response mechanism to GEJ resistance that is a part of normal esophagogastric junction mechanics, since our study showed a positive correlation between intrabolus pressure, peristaltic amplitude and residual GEJ relaxation pressure in all the groups we studied.

The impact of fundoplication on the strength of esophageal peristalsis has often been debated with some studies showing fundoplication increases distal esophageal peak pressure,[18,22–25] whilst others show a reduction or no change.[17,21,26] These studies were confined to observations in fundoplication patients without any comparison with other patient groups or normal subjects. Our study shows that esophageal contractile strength varies according to the degree of GEJ resistance to flow in both unoperated and operated persons.

We also assessed how a hiatus hernia might influence dysphagia and GEJ compliance. A small hiatus hernia was associated with low intrabolus, basal and residual GEJ relaxation pressures and these patients were more likely to experience dysphagia. A recent study found that hiatal hernia patients with reflux symptoms and no dysphagia had
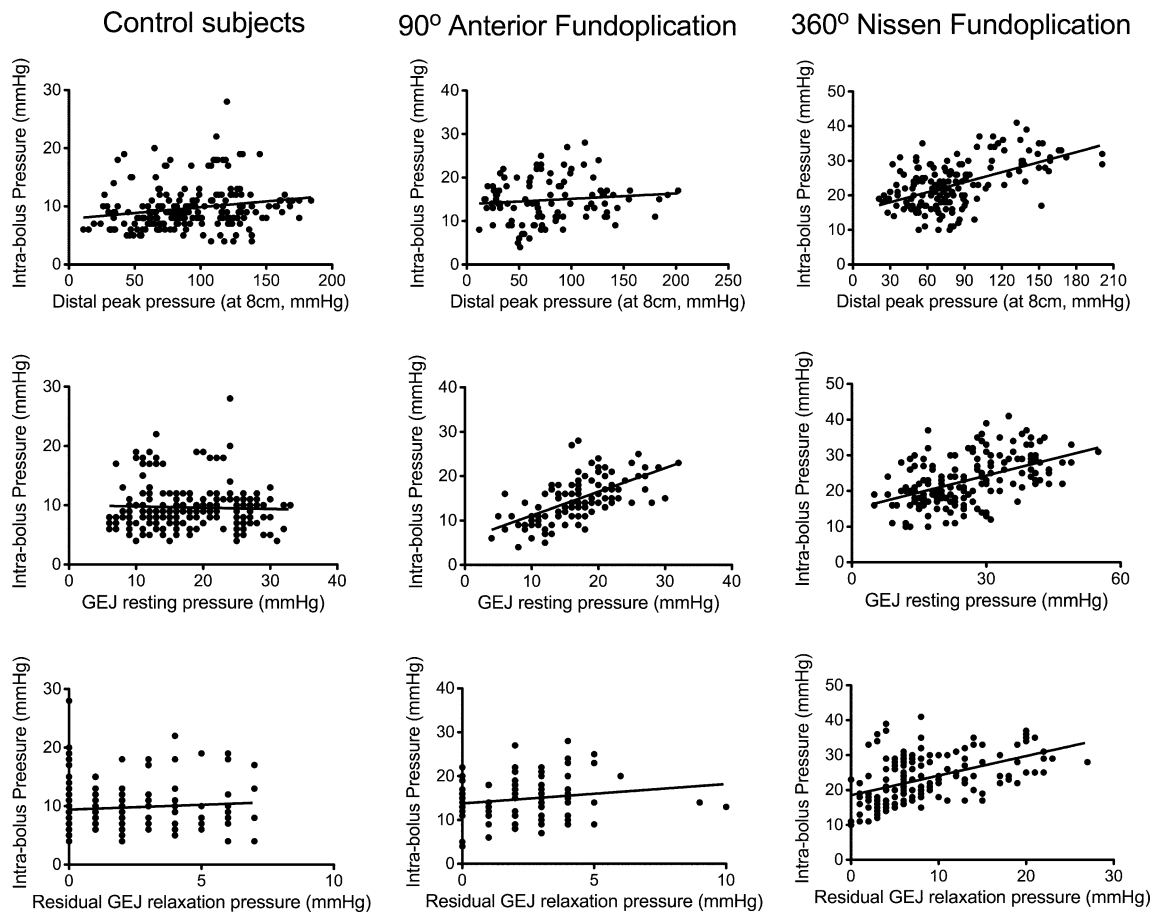
Fig. 4 Relationship of intrabolus pressure with peristaltic esophageal body peak pressure (*above bolus*) and GEJ pressures (*below bolus*)

lower intrabolus and residual GEJ relaxation pressure than hiatal hernia patients with dysphagia but no reflux.[27] Future studies need to assess whether the space the herniated stomach occupies in the hiatal canal may affect resistance to bolus transit through the GEJ and alter intrabolus pressure.

There are some limitations to our study. Patients undergoing surgery were not randomised for the type of fundoplication and gender bias was evident. This bias is probably due to the information we provide routinely to patients about the risks of fundoplication, notably that a total fundoplication carries a greater risk of increased flatulence than a partial fundoplication.[28] Women seem to be more concerned about this risk than men. From a technical perspective, we measured the distensibility of the relaxed GEJ indirectly and so are unable to assess the impact of GEJ opening diameter on intrabolus and residual GEJ relaxation pressure and the incidence of dysphagia. Previous studies have shown GEJ opening diameter during swallow-induced relaxation negatively correlates with intrabolus pressure and is related to the radial extent of fundoplication.[15] Our study findings are limited by the use of a water bolus that is well tolerated and safe, but may not emulate the conditions for the dysphagia most commonly

reported after fundoplication, namely dysphagia for solids. Further, we specifically excluded synchronous and nonpropagating esophageal contractions from the analysis. However, 91% of patients with reflux disease displayed ≥70% primary peristalsis whilst 42% had dysphagia.

The future is bright for addressing some of these limitations with recently established high resolution manometry (HRM).[29] HRM evaluation with a similar protocol and incorporating recent innovations for assessment of esophageal motor function[29,30] holds promise for better understanding of postoperative dysphagia, including the identification of individual patients at risk of this side effect. HRM studies combined with intraluminal impedance for recording bolus flow with a viscous or solid bolus is also a promising option.[31] Further, a relative 'new comer', the functional luminal imaging probe (FLIP), looks promising as a tool for measuring distension in the GEJ.[32]

Currently, the mechanical components of antireflux surgery, namely, hiatal repair and fundal wrap, cannot be separately identified with either a 6-cm sleeve sensor or the 1-cm spacing of pressure sensors in currently available solid state HRM catheters.[33] HRM needs to evolve further to enable even closer spatial arrangement of pressure

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Table 4 Predictors of intrabolus pressure

Predictor	Controls $N=22$	Reflux patients, no hiatus hernia $N=29$	Reflux patients with hiatus hernia $N=24$	Anterior 90° fundoplication $N=14$	Nissen 360° fundoplication $N=19$
	Intrabolus pressure (mmHg)				
	A 1 mmHg rise in each parameter, predicts a rise in intrabolus pressure of:				
Distal esophageal peak pressure	0.03* (0.01)	0.02† (0.01)	0.01¥ (0.01)	0.002 (0.01)	0.04* (0.01)
GEJ pressure	0.02 (0.03)	0.01† (0.04)	0.07 (0.04)	0.08 (0.08)	0.01 (0.04)
Residual GEJ relaxation pressure	0.02 (0.14)	0.25¥ (0.12)	0.25 (0.19)	0.32 (0.24)	0.30† (0.09)

Data are estimated increase in intrabolus pressure per 1 unit increase in predictor (mmHg)

GEJ, gastroesophageal junction. Linear mixed effects model, data are coefficient (std error); significance level:

* $p<0.001$

† $p<0.01$

¥ $p<0.05$

Table 5 Dysphagia and intraluminal pressures after fundoplication

Postoperative data	Dysphagia none $N=9$	Dysphagia before and after $N=11$	Dysphagia postop only $N=12$	P value†
Distal esophageal peak pressure, mmHg	104.9±10.3*	63.0±10.0*	72.2±9.6	**0.02†**
Intrabolus pressure, mmHg	20.1±2.2	16.0±2.0	22.1±2.0	0.11†
GEJ basal pressure, mmHg	20.0 (17–21)	15.0 (10–22)	20.0 (16–34)	0.33¥
Residual GEJ relaxation pressure, mmHg	4.4 (3.3–8.0)	2.5 (1.4–4.8)*	7.0 (3.6–10)*	**0.04***

GEJ, gastroesophageal junction. Data mean ± SEM or median (IQR). Per subject analysis; pooled data for both 90° fundoplication (14) and 360° fundoplication (19); the group with preop dysphagia only ($N=1$) was excluded from the analysis

† ANOVA with Bonferroni posttest

¥ Kruskal–Wallis with Dunn's posttest, $p<0.05$ between the * two groups

Significant differences shown in bold type

sensors (≤5 mm spacing) in the distal third of the catheter in the region used to record GEJ topographic pressures.

Conclusion

Our study establishes that intrabolus pressure and residual GEJ relaxation pressure are influenced by the extent of the fundoplication and that these are key manometric measures of GEJ compliance. In reflux disease, preoperative dysphagia is associated with suboptimal esophageal function (low distal esophageal driving pressure) and altered anatomy (hiatus hernia). Postfundoplication dysphagia is associated with reduced compliance of the GEJ caused by the new fixed component of the antireflux barrier, as well as low distal esophageal driving pressure. We propose the esophagus has an adaptive response for resistance to flow across the gastro-esophageal junction and limits in this adaptive response result in failure of bolus transit and dysphagia.

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5

SUSCEPTIBILITY TO DYSPHAGIA AFTER FUNDOPLICATION REVEALED BY NOVEL AUTOMATED IMPEDANCE MANOMETRY ANALYSIS

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Name of Principal Author (Candidate)	Jennifer C Myers
Contribution to the Paper	Co-conceived and designed the study; Recruited subjects and performed the investigations; Conceived novel approach for data analysis, Undertook conventional and novel analysis of physiological data; Performed statistical analysis and interpreted the study findings. Drafted the manuscript including critical revision and submission for publication.
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Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.
Signature	Date 3- 2, 16

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By signing the Statement of Authorship, each author certifies that:
   i.   the candidate's stated contribution to the publication is accurate (as detailed above);
   ii.   permission is granted for the candidate in include the publication in the thesis; and
   iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Name of Co-Author	Glyn G Jamieson
Contribution to the Paper	Supervised the development of the study; Performed or supervised antireflux surgery on study subjects; Contributed to critical revision and submission of the final manuscript.
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Contribution to the Paper	Developed software for novel data analysis, Performed or supervised novel analysis of the physiological data; Concieved and formulated dysphagia risk index; Assisted with interpretation of study findings; Contributed to drafting the manuscript, including critical revision and approval of the final manuscript.
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Susceptibility to dysphagia after fundoplication revealed by novel automated impedance manometry analysis

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Abstract

Background Conventional measures of esophageal pressures or bolus transport fail to identify patients at risk of dysphagia after laparoscopic fundoplication. **Methods** Liquid and viscous swallows were evaluated with impedance/manometry in 19 patients with reflux disease before and after surgery. A new method of automated impedance manometry (AIM) analysis correlated esophageal pressure with impedance data and automatically calculated a range of pressure and bolus movement variables. An iterative analysis determined whether any variables were altered in relation to dysphagia. Standard measures of esophago–gastric junction pressure, bolus presence time, and total bolus transit time were also evaluated. **Key Results** At 5 months postop, 15 patients reported some dysphagia, including 7 with new-onset dysphagia. For viscous boluses, three AIM-derived pressure–flow variables recorded preoperatively varied significantly in relation to postoperative dysphagia. These were: time from nadir esophageal impedance to peak esophageal pressure (TNadImp–PeakP), median intra-bolus pressure (IBP, mmHg), and the rate of bolus pressure rise (IBP slope, mmHg s^{-1}). These variables were combined to form a dysphagia risk index (DRI = IBP × IBP_slope/TNadImp–PeakP). DRI values derived from preoperative measurements were significantly elevated in those with postoperative dysphagia (DRI = 58, IQR = 21–408 vs no dysphagia DRI = 9, IQR = 2–19, P < 0.02). A DRI >14 was optimally predictive of dysphagia (sensitivity 75% and specificity 93%). **Conclusions & Inferences** Before surgery, a greater and faster compression of a swallowed viscous bolus with less bolus flow time relates to postoperative dysphagia. Thus, susceptibility to post-fundoplication dysphagia is related to a pre-existing sub-clinical variation of esophageal function.

Key words antireflux surgery, dysphagia, esophagus, impedance/manometry, laparoscopic fundoplication.

Abbreviations: EGJ, esophago-gastric junction; AIM, automated impedance manometry; IBP, intra-bolus pressure; Distal IBP slope, slope of the pressure rise associated with distal IBP; Distal TNadImp–PeakP, time between nadir impedance and peak pressure in distal esophagus; BPT, bolus presence time; TBTT, total bolus transit time; msu, median standardized units; DRI, dysphagia risk index; IQR, interquartile range.

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INTRODUCTION

Dysphagia after fundoplication is a common and sometimes disruptive problem.[1] Apart from technical errors and surgical complications, the cause of dysphagia after fundoplication remains unclear.[1] A modest reduction in the prevalence of dysphagia after fundoplication has been achieved through modifications to operative technique. Meta-analyses of outcomes sug-

gest a partial fundoplication results in less dysphagia and less revisional surgery than a total fundoplication.[2–4] Currently however, preoperative testing for esophageal pressures or bolus transport are unable to identify individual patients at risk of dysphagia after fundoplication.[5–8]

Bolus transit is a fundamental outcome of esophageal motor function and, logically, failed bolus transit would be expected in patients with dysphagia. Counterintuitively, synchronous contractions and failed peristalsis are frequently associated with complete bolus transit as recorded by intraluminal electrical impedance.[9,10] A preliminary analysis of our impedance data using conventional analysis,[7] and a similar study,[6] failed to identify aspects of either liquid or viscous bolus transport that predict postoperative dysphagia.[6] Thus, neither intraluminal pressures alone nor measures of bolus presence are adequate to determine susceptibility to fundoplication dysphagia.

Thus far, no analysis of postfundoplication dysphagia has derived variables from a combined evaluation of manometric and impedance recordings. Recently, a novel automated analysis method has been developed for processing pharyngeal impedance/manometry data and this approach revealed, for the first time, patterns of pharyngeal function associated with ineffective pharyngeal bolus clearance and aspiration risk.[11,12] The aim of this study was to determine whether the objective and reproducible analysis approach used in the pharynx[13] could be adapted to identify patients at risk of postfundoplication dysphagia. Accordingly, we modified the new method of analysis (now called automated impedance manometry, AIM) to assess esophageal function before and after partial and total fundoplication.

METHODS

Subjects

Twenty-one patients with reflux symptoms referred for preoperative assessment were invited to undergo combined esophageal impedance/manometry testing with symptom assessment prior to and 5 months after fundoplication. Two patients did not complete the study protocol (1 patient was withdrawn following a cerebrovascular accident; the other declined intubation). Thus, 19 patients (10 male; mean age = 50.9 years, range = 29–78 years) were studied. Erosive or ulcerative esophagitis, and/or positive 24 h pH monitoring (% time <pH4 greater than 4%) were considered proof of reflux disease. No patient had a primary esophageal motility disorder such as scleroderma or achalasia, a hiatus hernia >5 cm, or previous antireflux surgery. Prior to surgery, all 19 patients experienced heartburn (100%) and most experienced regurgitation (95%). The type of operation, 90° or 360° fundoplication, was determined by informed patient

preference. All subjects gave written informed consent. The Research Ethics Committee of the Royal Adelaide Hospital approved the protocol, which was performed in accordance with Australian NH&MRC guidelines.

Measurements

Assessment of dysphagia A validated dysphagia composite score documented difficulty with swallowing, with a frequency of 'always', 'sometimes', or 'never' for nine food types with increasing viscosity (water to meat; scale 0–45).[14] All patients underwent a barium swallow on day 1 and 5 months after surgery (same day as impedance/manometry) to identify anatomical abnormalities (recurrent hiatal hernia; wrap migration). Patients with postoperative dysphagia requiring endoscopy ± dilatation or revisional surgery were deemed to have persistent dysphagia.

Impedance/manometry Esophageal pressures and intraluminal electrical impedance were recorded using an eight-channel water-perfused catheter (0.3 mL min^{-1}) with four paired impedance rings. Manometric side holes, four at 5 cm intervals above the esophago–gastric junction (EGJ), were matched with four pairs of 4-mm long electrical impedance rings built into the catheter, 2 cm apart, above and below each side hole. A 6-cm sleeve was positioned across the EGJ; the most distal side hole recorded gastric pressure, and the most proximal side hole at 29 cm above the EGJ monitored pharyngeal contractions of swallow initiation (air perfused, 16 mL min^{-1}). Each impedance electrode was activated by a high-frequency (1 kHz) low-amplitude alternating current ($<6 \mu A$). Manometric and impedance data were recorded simultaneously using commercial hardware and software (Insight Acquisition; Sandhill Scientific, Highland Ranch, CO, USA).[15]

Proton pump inhibitors were ceased 5 days prior to testing. After a 6-h fast, the impedance/manometry assembly was passed transnasally following topical nasal anesthesia (5% lignocaine HCl). With patients in the right lateral position, the sleeve was positioned across the EGJ with catheter secured at the nose. A 10-min rest period was followed by: ten 5-mL liquid swallows (normal saline) and ten 5-mL viscous swallows (a low-impedance EFT-viscous swallow challenge medium; Sandhill Scientific) given at 30-s intervals.

Data analysis

Data were evaluated by conventional analysis and by the new AIM analysis. Investigators blinded to clinical outcome undertook the data analysis.

Conventional analysis of manometry and impedance data Using the BIOVIEW software (v 5.3.4; Sandhill Scientific), EGJ basal and residual (minimum) relaxation pressure on swallowing were measured at end-expiration and referenced to gastric pressure (mmHg). The peak esophageal contraction amplitude (mmHg) and intra-bolus pressure (IBP, mmHg, maximum or plateau pressure prior to peristaltic upstroke), both referenced to end-expiratory esophageal baseline, were determined for each bolus swallow.[16]

For the evaluation of esophageal bolus transport, the bolus presence time (BPT, s) was determined as the interval between the bolus entry time (50% drop from 3-s preswallow basal impedance) and the bolus exit time (recovery to 50% of basal impedance for longer than 5 s). The total bolus transit time (TBTT, s) was the interval from bolus entry at the proximal paired impedance rings to bolus exit at the most distal paired impedance rings. If BPT or TBTT was ≥30 s, this was recorded as 30 s. Abnormal bolus

clearance was defined as TBBT ≥15 s for liquids, TBBT >17 s for viscous , and BPT outside the normal range at any level in the esophagus,[15] or when bolus exit was not identified at any of the three distal impedance segments.[10] Patients were considered to have normal esophageal transit if ≥80% liquid and ≥70% viscous swallows showed normal bolus clearance.[10,15]

AIM analysis Raw manometric and impedance data over a 30-s window for each test bolus were exported in ASCII text format, then analyzed using MATLAB (version 7.9.0.529 R2009b; Math-Works, Inc., Natick, MA, USA). Pressure and impedance data were smoothed by a cubic interpolation method in which temporal data were doubled and spatial data increased by a factor of 10,[11] achieving a virtual increase in data sampling from 1 value per 5 cm sampled at 30 Hz to 10 values per 5 cm sampled at 60 Hz (Fig. 1A). The raw impedance data were standardized and reported as median standardized units (msu) rather than ohms.[11]

Derivation of pressure–flow variables The spatial–temporal patterns of esophageal peristaltic pressure and bolus movement across the 4 pressure–4 paired impedance array were analyzed in separate pressure–impedance plots with algorithms that made the analysis easy to perform (Fig. 1B). For each swallow, a 30-s plot that centered around the peristaltic wave was exported and the peristaltic sequence (from swallow onset to EGJ) was automatically analyzed. At all positions along the plot, the analysis algorithm identified the peak of the peristaltic wave and then the nadir impedance preceding the peak. Using these pressure and impedance landmarks, the time interval between nadir esophageal impedance (TNadImp, s) and peak esophageal pressure (TPeakP, s) was automatically determined at all positions along the imped-ance–pressure array (Fig. 1B). Accordingly, TNadImp and TPeakP reflect the rate of bolus movement and peristaltic propagation. The time from nadir impedance to peak pressure (TNadImp–PeakP, s) measured the relationship between the centre of the bolus during maximal esophageal distension and the peristaltic peak pressure. Esophageal pressures during swallowing were referenced to preswallow esophageal baseline pressures. Guided by TNadImp and TPeakP, the following variables were also determined automatically using algorithms and averaged for both the entire and distal half of impedance–pressure array: (i) pressure at TNadImp (PNadImp, mmHg) (Fig. 1C); (ii) pressure at TPeakP (PeakP, mmHg) (Fig. 1C); (iii) IBP (mmHg), estimated by calculating the median pressure recorded from NadImp to the midpoint in the time of TNadImp–PeakP (Fig. 1D); and (iv) IBP slope, defined as the change in pressure over time from PNadImp to the pressure at midpoint of TNadImp–PeakP (IBP slope, mmHg s^{-1}).

Derivation of EGJ pressures The cumulative duration of EGJ relaxation was plotted from minimum to maximum pressure and used to calculate the 4-s integrated relaxation pressure.[17] Resting EGJ pressure (mmHg) was recorded for 10 s prior to EGJ relaxation onset. EGJ pressures were referenced to gastric pressure.

Derivation of dysphagia risk index The iterative analysis revealed three esophageal pressure–flow variables for preoperative viscous swallows that were significantly associated with postfundoplication dysphagia (see Results). These three variables were combined to form an index so as to amplify these differences. This approach was based on a similar analytical approach used for pharyngeal impedance/manometry data.[11,12] High values (IBP) were divided by small values (TNadImp–PeakP) to give a single parameter with
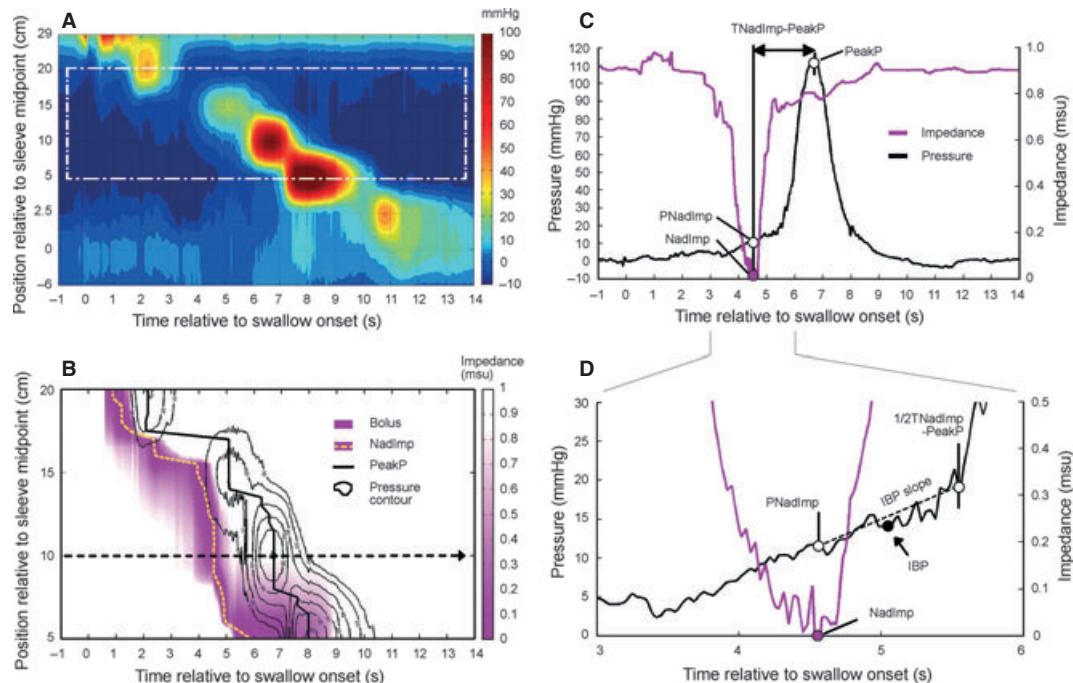

Figure 1 Calculation of pressure–flow variables. A color contour plot of intraluminal pressures for a viscous bolus swallow (A), from which a region of interest was selected, converted to contour lines, then overlaid with impedance data (B). Automated processing identified from the pressure data, the time of peak pressure (black line), and from impedance data (purple), the time of nadir impedance (yellow dash line), throughout the array (B). The time of peak pressure (tPeakP) and nadir impedance (TNadImp) (C) were reference points for algorithms (B, C; combined impedance/manometry data at black dash line are expanded in C and D) that defined: time between nadir impedance and peak pressure (TNadImp–PeakP), pressure at nadir impedance (PNadImp), peak pressure (PeakP) (C), and median intra-bolus pressure (IBP) and IBP slope (D).

a wider numeric scale. The combined variables form the esophageal dysphagia risk index (DRI) by the formula: IBP multiplied by slope of IBP rise in the distal esophagus, divided by the time interval between the nadir impedance and peak pressure in the distal esophagus.

$$DRI = (IBP \times Distal\_IBP\ slope)/(Distal\_TNadImp-PeakP).$$

The DRI was calculated for pre- and postoperative viscous and liquid bolus swallow data. Further, DRI was evaluated for patients according to their pattern of dysphagia: patients with (i) no dysphagia either pre- or 5 months postoperatively; (ii) dysphagia before and after fundoplication; and (iii) dysphagia postop only.

Additionally, the clinical relevance of DRI values obtained for patients with reflux disease was explored by comparing these data with data from healthy control subjects (24 subjects, 16 male; age = 48.2 ± 2.9 years). The healthy control subjects from Adelaide (n = 24) were part of a collaborative study between Adelaide and Utrecht.[15] All control subjects were free of dysphagia and experienced no gastrointestinal symptoms.

Laparoscopic fundoplication

All operations were performed laparoscopically with the creation of either a loose 2-cm-long 360° fundoplication[18] or an anterior 90° partial fundoplication[19] as previously described.

Statistical analysis

In each patient, the mean of 10 liquid and 10 viscous swallows for each variable is reported. Patient group data for normally distributed data are presented as mean ± SE and for non-parametric data, the median with interquartile range (IQR). Paired data before and after surgery were compared using Wilcoxon signed-ranks test or paired t-test. Significance was initially set at $P \leq 0.10$ for descriptive data to identify parameters of interest and $P < 0.05$ for pressure–flow variables described above. The analysis of variance testing, ANOVA or Kruskal–Wallis, with multiple comparison *post hoc* Dunn's or Holm–Sidak method, was applied for comparison of patients grouped by dysphagia status. For this analysis, a patient was positive for dysphagia when their dysphagia composite score was >0. Sensitivity and specificity were determined for pressure–flow variables and DRI. The Cohen's kappa statistic is reported, where kappa value of 0.00 represents no agreement, 0.00–0.20 slight, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 substantial, and 0.81–1.00 near-perfect agreement.

RESULTS

Total fundoplication was performed in 8 patients and a partial fundoplication in 11 patients. Surgery was efficacious with 95% of patients experiencing less heartburn (no heartburn 13/19, reduced heartburn 5/19, and similar heartburn 1/19 patients) and 84% experiencing less regurgitation (16/19 patients).

Dysphagia before and after fundoplication

At study entry before surgery, 8 of 19 patients (42%) experienced some dysphagia with a median dysphagia composite score of 0, IQR = 0–13.5. Dysphagia was mostly for solids only, with patients experiencing dysphagia 'sometimes' for eggs, fish, bread, apple, and steak. Five months after surgery, 15 patients reported dysphagia (79%), including 7 with new-onset dysphagia (Fig. 2). Overall, more patients reported dysphagia after fundoplication, but the median composite dysphagia score was not significantly higher (0, IQR = 0–13.5 preop *vs* 4, IQR = 1–15 postop; $P = 0.28$). Seven of 15 patients reported a postoperative dysphagia score <5 out of a possible 45 (this equates to experiencing occasional dysphagia for one food type, either bread, apple, or steak). Problematic dysphagia after surgery was rare with only two patients requiring endoscopic dilatation for dysphagia, one at 6 months after surgery (no relief of symptoms; declined further intervention; note: high DRI preop and postop) and another at 17 months (good relief of symptoms; note: low DRI preop and postop). No abnormality was identified at endoscopy and no patient underwent revisional surgery.

Barium swallows on day 1 and 5 months after surgery showed that the fundoplication was intact and sub-diaphragmatic with no evidence of herniation in all patients except one. For this patient, there was evidence of wrap migration 24 h after surgery, which was surgically corrected the same day with mesh repair of the hiatus. A repeat barium swallow another 24 h later and 5 months subsequently were unremarkable.

Effects of fundoplication on esophageal function

Baseline measurements showed that 4 of 19 (21%) patients had abnormal esophageal transit preoperatively (see Methods). Liquids traversed the esophagus more quickly than viscous boluses (preop TBTT 5.6 ± 0.3 s liquid *vs* 7.5 ± 0.7 s viscous, $P < 0.02$) and EGJ pressures were low, consistent with reflux disease (Tables 1 and 2).
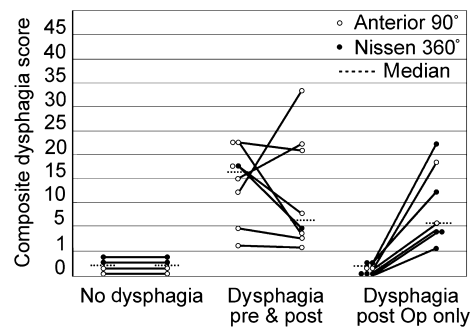

Figure 2 Composite dysphagia scores before and after fundoplication.

Table 1 Impedance parameters using conventional analysis before and after fundoplication

Esophageal flow	Liquid bolus $n = 19$			Viscous bolus $n = 19$		
	Preop	Postop	*P*-value	Preop	Postop	*P*-value
Bolus presence time, s*						
At 20 cm	2.1 (1.6, 2.5)	2.9 (1.9, 5.1)	<0.01	2.0 (1, 3.5)	2.9 (1.7, 5.7)	0.02
At 15 cm	3.0 (2.3, 3.5)	4.4 (3.6, 6.0)	0.001	3.3 (2.6, 4.2)	4.2 (3.2, 6.3)	<0.02
At 10 cm	3.9 (3.6, 4.4)	6.0 (4.6, 7.3)	0.001	3.4 (2.9, 4.9)	4.8 (3.5, 7.3)	0.05
At 5 cm	5.0 (4.4, 5.8)	7.1 (6.0, 8.7)	<0.001	4.5 (3.0, 7.1)	6.7 (4.1, 12.3)	<0.01
Total bolus transit time, s	5.5 (4.8, 6.5)	8.0 (7.0, 9.6)	<0.01	7.5 ± 0.7	11.3 ± 1.3	<0.02
Complete bolus clearance (%)†	100 (90, 100)	80 (55, 90)	<0.001	100 (80, 100)	80 (50, 100)	<0.01
Abnormal bolus clearance (%)†	0 (0, 10)	20 (10, 45)	<0.001	0 (0, 20)	20 (0, 50)	<0.01

*Bolus presence time for paired impedance rings at a distance above EGJ.
†See Methods section for criteria of normal and abnormal bolus clearance. Paired data before and after surgery were compared using Wilcoxon signed-ranks test or paired *t*-test.

Table 2 Automated analysis of pressure–flow variables in the distal esophagus and EGJ before and after fundoplication

Variable	Liquid bolus $n = 19$			Viscous bolus $n = 19$		
	Preop	Postop	*P*-value	Preop	Postop	*P*-value
Distal esophageal						
PeakP, mmHg	52 ± 5	61 ± 7	0.16	45 ± 4	54 ± 6	0.14
PNadImp, mmHg	6 (3, 7)	6 (4, 10)	0.29	5 (4, 8)	9 (3, 23)	0.08
IBP, mmHg	6 ± 1	11 ± 2	0.10	10 ± 2	16 ± 3	0.09
IBP slope, mmHg s^{-1}	2 (1, 5)	4 (1, 19)	0.21	7 ± 1	9 ± 2	0.19
TNadImp–PeakP	2.7 ± 0.3	3.1 ± 0.3	0.15	2.9 ± 0.3	2.4 ± 0.3	0.10
EGJ pressure during 10 s prior to swallowing						
Basal EGJ pressure, mmHg	7 (4, 15)	17 (9, 27)	0.01	8 ± 2	23 ± 5	0.02

Distal esophageal, measure of the variable in the distal half of the pressure–impedance array; PeakP, peak peristaltic pressure; PNadImp, pressure at nadir impedance; IBP, intra-bolus pressure; IBP slope, slope of the pressure rise associated with IBP; TNadImp–PeakP, time between nadir impedance and peak pressure; EGJ, esophago-gastric junction. Paired data before and after surgery were compared using Wilcoxon signed-ranks test or paired *t*-test.

Following fundoplication, there was significantly slower esophageal clearance of liquid and viscous boluses (Table 1), with a sequential increase in BPT as the bolus traversed the esophagus, leading to longer transit time. Surgery led to a shift from normal to abnormal esophageal transit (see Methods) in a third of patients (6/19). One patient with abnormal transit preoperatively showed normal transit postoperatively. A total of 9 of 19 (47%) patients showed abnormal esophageal transit after surgery.

EGJ manometric variables were significantly altered by surgery, consistent with fundoplication increasing intraluminal pressure at the level of the EGJ (Table 2, see Appendix S1). In particular, conventional IBP was significantly higher after fundoplication for both liquid and viscous swallows, reflecting greater resistance to flow at the EGJ during swallowing. Other conventional and new variables of esophageal function were generally unchanged by surgery (Table 2, see Appendix S1).

Preoperative impedance/manometry data and dysphagia after surgery

Data were explored to determine whether any variables were altered in relation to dysphagia. For data collected prior to surgery, EGJ pressures and the bolus clearance measures, BPT, and TBTT bore no relationship to postoperative dysphagia for both liquid and viscous swallows.

The AIM analysis of preoperative data revealed three pressure–flow variables for viscous boluses that varied significantly with regard to dysphagia (Table 3). Patients with postoperative dysphagia had significantly greater IBP, IBP_slope, and significantly shorter TNadImp–PeakP preoperatively compared with those without dysphagia after surgery. With liquid boluses, only preoperative TNadImp–PeakP was significantly shorter in patients with postoperative dysphagia.

Table 3 Viscous bolus swallow data before and after surgery by dysphagia status after surgery

Variable	Preop viscous bolus $n = 19$			Postop viscous bolus $n = 19$		
	No dysphagia postop	Dysphagia postop	P-value	No dysphagia postop	Dysphagia postop	P-value
Esophageal						
Peak P, mmHg	44 (40, 52)	48 (41, 62)	0.45	68 ± 5	44 ± 4	**0.011**
PNadImp, mmHg	11 (6, 13)	15 (7, 23)	0.29	6 (3, 11)	14 (9, 17)	0.06
IBP, mmHg	10 (7, 13)	18 (12, 20)	0.032	10 ± 1	18 ± 3	0.17
Distal_IBP, mmHg	3 (−2, 7)	8 (5, 15)	0.08	9 ± 2	17 ± 3	0.24
Distal_IBP slope, mmHg s^{-1}	2 ± 1	9 ± 1	0.048	8 ± 2	10 ± 2	0.77
Distal_TNadImp–PeakP, s	4.0 ± 0.3	2.6 ± 0.3	0.027	3.2 ± 0.7	2.1 ± 0.3	0.13
Dysphagia risk index	9 (−2, 19)	58 (21,408)	0.014	33 (8, 61)	42 (2, 369)	0.47

Distal, measure of this variable in the distal half of the pressure–impedance array; IBP, intra-bolus pressure; IBP slope, slope of the pressure rise associated with IBP; TNadImp–PeakP, time between nadir impedance and peak pressure. Data were compared using Mann–Whitney test or t-test.

Dysphagia risk index

The three aforementioned pressure–flow variables identified by the AIM analysis contributed to the DRI (see Methods). For viscous swallows, median preoperative DRI was significantly higher in patients with dysphagia after surgery, compared with those without postoperative dysphagia (Table 3). By contrast, for liquid boluses, the median preoperative DRI was not significantly different between those with and without dysphagia after surgery, although trends were observed.

Further evaluation found DRI was the highest in patients with 'new-onset' dysphagia after surgery (Table 4). The DRI for patients with dysphagia both before and after surgery was significantly higher than control subjects (Table 4). The three esophageal variables showed high sensitivity and specificity (Fig. 3). Based on these data, optimal predictive value for DRI is >14 with a sensitivity of 75%, a specificity of 93%, and kappa statistic of 0.68, i.e., substantial agreement (Fig. 3). DRI has better predictive power than the individual parameters. The simpler combination of IBP multiplied by Distal_IBP slope was significantly

elevated in patients with dysphagia (135, IQR = 51–227 vs no dysphagia 27, IQR = −7–48, P = 0.01). However, this combination had no predictive value for postoperative dysphagia (sensitivity = 50%, specificity = 14%, kappa statistic = 0.00, i.e., no agreement).

Preoperative impedance/manometry data and dysphagia prior to surgery

For patients with dysphagia prior to surgery, preoperative TBTT and BPT (except viscous BPT at 20 cm above EGJ) were not significantly different for liquid or viscous swallows compared to those without preoperative dysphagia. EGJ intraluminal pressures and IBP did not vary significantly by dysphagia status.

The AIM analysis of patients with dysphagia prior to surgery showed that only preoperative PeakP for viscous boluses was significantly lower in patients with dysphagia (31 mmHg, IQR = 4–45 vs 51 mmHg, IQR = 39–68, P = 0.02). For preoperative viscous bolus data, DRI for the presence/absence of dysphagia before surgery did not reach statistical significance. Some trends were observed for responses to liquid boluses:

Table 4 Viscous bolus swallow data for control subjects and for reflux patients before surgery by dysphagia status

Viscous bolus data before surgery	Healthy control subjects $n = 24$	No dysphagia preop or postop $n = 4$	Dysphagia preop and postop $n = 8$	Dysphagia postop only $n = 7$	P-value
IBP, mmHg	6 (4, 7)	10 (7, 13)	19 (12, 26)[†]	16 (12, 30)[†]	**<0.001**
Distal_IBP slope, mmHg s^{-1}	4 (3, 7)	3 (−1, 4)	7 (3, 10)	5 (5, 14)[*][†]	**0.022**
Distal_TNadImp–PeakP, s	3.7 ± 0.1	4.0 ± 0.3	2.7 ± 0.4[†]	2.4 ± 0.4[†]	**0.002**
Dysphagia risk index	6 (3, 13)	6 (−2, 19)	40 (16,97)[†]	94 (23, 600)[*][†]	**<0.001**

Distal, measure of this variable in the distal half of the pressure–impedance array; IBP, intra-bolus pressure; Distal_IBP slope, slope of the pressure rise associated with IBP in the distal esophagus; TNadImp–PeakP, time between nadir impedance and peak pressure. P-values are for Kruskal–Wallis one-way ANOVA on ranks or one-way ANOVA, with *post hoc* multiple comparison procedures, Dunn's method or Holm–Sidak method ([*]pairwise P < 0.05 vs no dysphagia; [†]pairwise P < 0.05 vs controls).
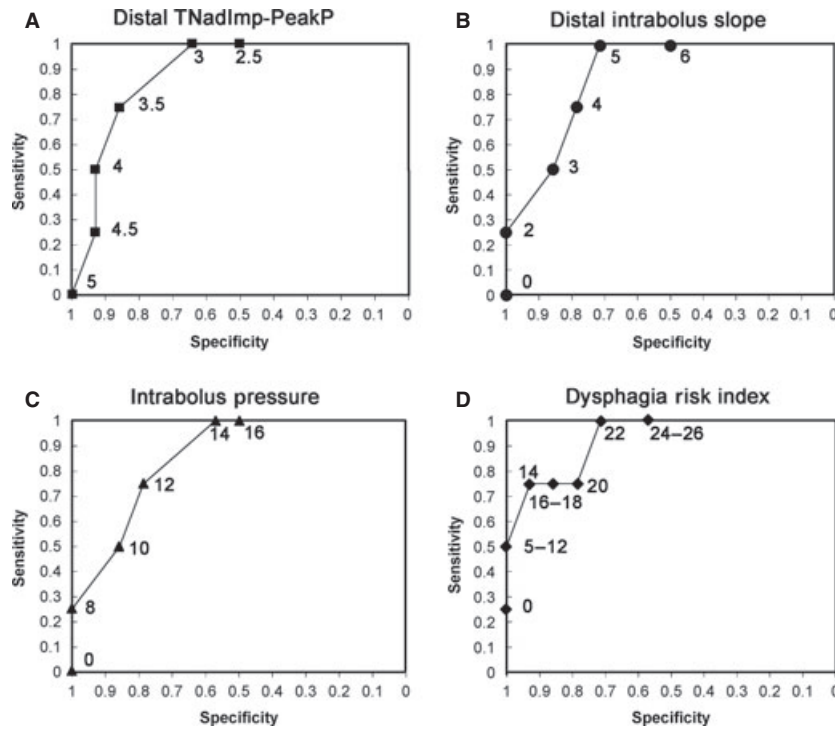
Figure 3 Sensitivity and specificity curves for (A) Distal TNadImp–PeakP, the time between nadir impedance and peak pressure in the distal esophagus; (B) Distal IBP slope, the slope of the pressure rise associated with distal intra-bolus pressure; (C) median intra-bolus pressure; and (D) the calculated dysphagia risk index.
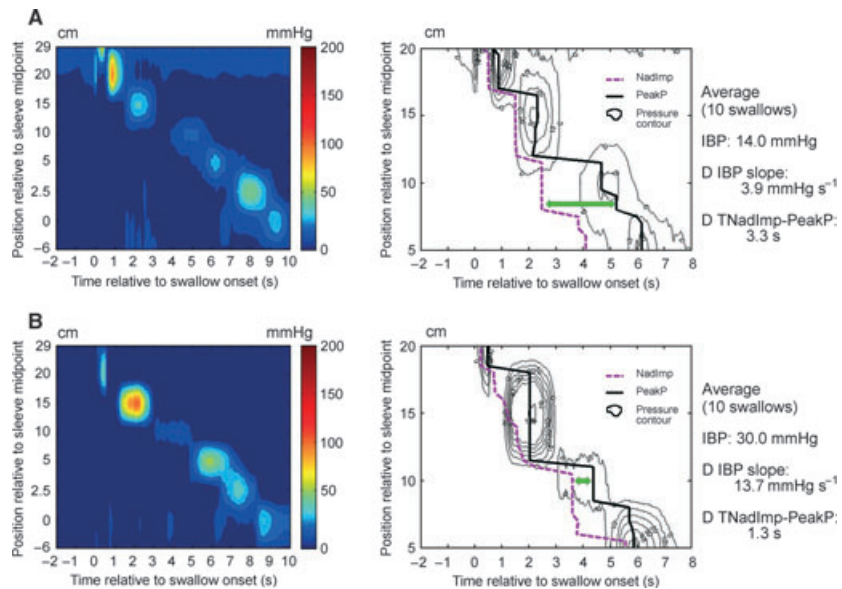

Figure 4 Images from the AIM analysis of preoperative viscous bolus swallows with color contour plot (left) and combined impedance/manometry data (right). Of specific interest (right image) is the pattern of the mean PeakP (black line) and mean nadir impedance (purple dashed line) in the distal esophagus with Distal_TNadImp–PeakP interval shown as a long double-headed green arrow for (A) a patient with no dysphagia before or after surgery in which preoperatively the mean DRI = 16 (low). This contrasts with an image for (B) a patient with new-onset dysphagia after surgery in which preoperatively the mean DRI = 330 (high) with a shorter Distal_TNadImp–PeakP interval (small double-headed green arrow), illustrating a different spatio–temporal relationship between esophageal peristaltic pressures and bolus movement present before surgery in a patient who developed dysphagia after fundoplication.

patients with dysphagia tended to show greater IBP in the distal esophagus (8 mmHg, IQR = 4–13 vs 5 mmHg, IQR = 3–7, P = 0.05) and shorter TNadImp–PeakP (3.1 ± 0.4 vs 4.0 ± 0.3 s, P = 0.07) compared to patients without dysphagia. However, the DRI for liquid boluses between patients with or without preop dysphagia did not reach statistical significance (12, IQR = 1–69 with dysphagia vs 2, IQR = 0–15 no dysphagia).

Postoperative impedance/manometry data and dysphagia after surgery

Although postoperative testing showed that BPT and TBTT were significantly longer (Table 1), these measures did not correlate with dysphagia after surgery. Interestingly, after surgery nine patients (9/19) had abnormal esophageal transit (see Methods) and 89% (8/9) were positive for dysphagia; however, of 10 patients (10/19) with normal esophageal transit, 70% (7/10) also reported dysphagia (Fisher exact test, P = 0.58). EGJ intraluminal pressures, although altered by fundoplication (Table 2, see Appendix S1), did not vary according to the presence of dysphagia after surgery.

The AIM analysis of postoperative data showed that viscous bolus esophageal PeakP was significantly lower in patients who developed postop dysphagia (44 ± 4 vs 68 ± 5 mmHg, P = 0.01). Similarly, liquid bolus esophageal PeakP showed a trend for being lower in patients with dysphagia (48 ± 5 vs 66 ± 4 mmHg, P = 0.07). Other pressure–flow variables, abnormal esophageal transit, and DRI for either bolus type did not differ significantly with regard to dysphagia.

Effects of hiatus hernia and degree of fundoplication

Prior to surgery, a small hiatus hernia <5 cm was identified in eight patients, but neither DRI, AIM, nor conventional variables were significantly different in the presence of a small hernia.

DRI for postoperative liquid and viscous swallows did not vary significantly in relation to the type of fundoplication, i.e., partial and total fundoplication. Fundoplication significantly raised both EGJ residual pressure during swallowing and distal IBP, consistent with increased impediment to flow across the junction (total > partial fundoplication, see Appendix S2). Although surgery generally prolonged BPT at all esophageal segments and TBTT for liquid and viscous boluses for both types of fundal wrap (see Appendix S3), there was no significant difference between the

wrap types and there was no correlation with dysphagia.

DISCUSSION

In this study, a new method AIM analysis, which correlates manometric with impedance data, identified pressure–flow variables that were altered prior to surgery in patients who developed new-onset dysphagia following fundoplication. Our study indicates preoperative derivation of the DRI for viscous boluses will help identify patients at risk of postfundoplication dysphagia.

The search for an objective test to assess the likelihood of new-onset dysphagia after fundoplication has, till now, failed,[5,8] perhaps in part due to the use of liquid boluses for testing, when postfundoplication dysphagia is mostly for solids. However, it is important to recognize that, in the current study, manometry alone did not predict new-onset dysphagia irrespective of whether a liquid or viscous bolus was used. In addition, the current and previous studies[6] have shown that if only intraluminal impedance is evaluated, this fails to predict postoperative dysphagia even with the use of a viscous bolus.

In this study, the AIM analysis revealed new variables that better describe the subtleties of interactions between bolus movement and pressure patterns within the esophageal lumen. We found that median IBP, IBP slope, and TNadImp–PeakP relate to dysphagia. Median IBP and IBP slope reflect not only the compression of bolus between the EGJ and the peristaltic wave,[20] but also the speed at which the bolus moves and the level in the esophagus that the bolus is most compressed. Preoperatively, the rate of pressure rise within the swallowed bolus was faster in patients with postoperative dysphagia, shown by a higher IBP slope. TNadImp–PeakP reflects the location and timing of bolus presence during maximal esophageal distension, or the centre of the bolus relative to the time of peak pressure. Preoperative testing revealed that this time interval between nadir impedance to peak peristaltic pressure was significantly shorter in patients who developed dysphagia after surgery. This indicates that there was a pre-existing pressure–flow pattern: the centre of a swallowed bolus arrived later (i.e., relative to swallow onset) and was closer to the peak of the pressure wave; resulting in the bolus being more highly pressurized to facilitate passage through the esophagus (Fig. 4). This is a new paradigm for characterizing bolus movement, shifting from variables describing the spread of a bolus (BPT and TBTT) to variables

that describe the compression and drive of a bolus (IBP and TNadImp–PeakP).

This is the first report that shows how preoperative spatio–temporal relationships between esophageal pressure and bolus movement relate to postoperative dysphagia. Montenovo *et al.* utilized impedance/manometry, whereas Scheffer *et al.* used high-resolution EGJ manometry with fluoroscopy; both failed to find any preoperative measures of pressure and flow through the esophagus and EGJ that relate to postfundoplication dysphagia.[6,21] Notably, these studies relied on separate analyses of pressure and flow and the latter study was further limited by the use of only two esophageal body manometric recording points. In contrast, our approach to data analysis brings a new way of measuring esophageal function, of which some variables relate to dysphagia. In our study, variables such as IBP and peak peristaltic pressure were measured differently from previous studies. The median IBP as calculated by the AIM analysis brings focus to the magnitude of the IBP when the bolus is most compressed (see Fig. 1D). In a similar way, others report 'peak' esophageal pressure at a specific level in the esophagus (e.g., PeakP at 8 cm above EGJ), whereas the AIM analysis detects the peak esophageal pressure at any level in the esophagus for the peristaltic sequence.

The new pressure–flow variables from the AIM analysis were identified through algorithms for automatic recognition of signature pressure–flow characteristics inherent to all swallows. Esophageal AIM analysis was specifically developed for this study. It has built on the first use of this analysis method for the evaluation of pharyngeal swallowing, which derived a measure of pharyngeal swallow effectiveness and risk for aspiration.[11,12] The esophageal AIM analysis uses a similar iterative analysis approach to examine a range of pressure–flow variables for association with dysphagia. The AIM analysis with DRI calculation preoperatively is proof of concept for our analysis approach and shows that an individual's risk of fundoplication dysphagia can be defined before surgery.

In our study, DRI showed better predictive power than the individual variables and the potential prognostic value of DRI for the prediction of new-onset dysphagia is encouraging. Further studies are required to confirm the value of DRI in this clinical group, as well as its utility as a global measure of esophageal propulsive function. In this study, patients experienced low–moderate grade dysphagia after both types of fundoplication despite technically efficacious surgery, and yet in this setting DRI carried prognostic value for predicting postfundo-plication dysphagia, despite our use of relatively low spatial resolution recording methods. This suggests that the DRI is a sensitive index, which is not critically dependent on the spatial resolution of the impedance/manometry recording. Rather, it appears that direct correlation of impedance relative to pressure is the critical factor for the recognition of dysphagia risk. Thus, AIM analysis techniques could be clinically useful when applied to data of either low- or high-resolution impedance/manometry systems. Although high-resolution systems are state-of-the-art, low-resolution systems are still in wide use, especially in settings where the purchase and maintenance costs of high-resolution systems are prohibitive. We are now investigating the possibility that high-resolution impedance/manometry recordings might improve the recognition of patients at risk for postfundoplication dysphagia.

In our study, preoperative viscous bolus IBP, IBP slope, and TNadImp–PeakP were significantly associated with dysphagia after surgery. Preoperatively, these parameters for liquid swallows show a similar trend for preoperative dysphagia. Similarly, postoperative parameters trend for postoperative dysphagia. The trends indicate further studies are warranted and greater patient numbers will likely overcome a possible type II error. In support of this view, a comparison between our patients and healthy controls showed patients with dysphagia preoperatively had higher DRI before surgery than control subjects. Further, our findings suggest that fundoplication uncovers what might be called a sub-clinical esophageal dysfunction in patients presenting with new-onset postoperative dysphagia.

That the most significant findings in this study were for viscous swallows highlights the fact that liquid and viscous boluses flow through the esophagus differently. Liquid boluses are dispersed more widely through the esophagus and flow along it more quickly than viscous boluses.[10] The noted sequential increase in BPT as the bolus traverses the esophagus is in line with current understanding that a swallowed bolus accumulates in the bottom of the esophagus whereas the propulsive forces of peristalsis lead to an increase in IBP.[20,22] The current study suggests that the compact movement of a viscous bolus is a better stimulus for revealing the subtleties of interactions between bolus movement and intraluminal pressures.

This study has several limitations. Although the DRI was found to distinguish patients with new-onset dysphagia after surgery from patients with either persistent dysphagia or no dysphagia, our study involved a relatively small cohort. Our study was also underpowered to adequately explore the influence of

secondary factors such as the existence of dysphagia prior to surgery, hiatus hernia, and type of fundoplication. Despite these limitations, our analyses demonstrate the clinical relevance of describing bolus movement relative to esophageal pressures as captured by the calculation of the DRI.

Automation and objectivity are significant attributes of AIM analysis, as well as the derivation of new variables for bolus movement relative to esophageal pressure generation. This contrasts with separate analyses of bolus flow and luminal pressures. The AIM analysis avoids the pitfalls of manual analysis, such as categorical classifications and operator-dependent interpretation, e.g., intraluminal pressures classified by predefined 'normal values' or changes in impedance dependent on an arbitrary 50% cut-off criteria.[23,24] Automation yields variables that are impractical to derive manually and vastly reduces the time required for the analysis.

In conclusion, we present novel findings from esophageal AIM analysis that indicate that a patient's individual risk of developing postfundoplication dysphagia can be assessed prior to surgery. Future studies with high-resolution impedance/manometry are needed to further validate and calibrate this innovation.

DISCLOSURE

Dr. Omari is a technology consultant to Sandhill Scientific.

AUTHOR CONTRIBUTION

JCM conceived the study concept and design, and co-ordinated subject recruitment, participation, and follow-up; JCM, KC, and NQN performed the studies and analyzed data; GGJ performed or supervised surgery; TIO developed automated analysis concept and design, including analysis algorithms; JCM, JEVH, and TIO performed statistical analysis; JCM, JD, and TIO drafted the manuscript; JCM, JD, GGJ, TIO, NQN, RHH, KC, and JEVH contributed to critical revision of the manuscript and approval of the final version.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Esophageal luminal pressures using conventional analysis before and after fundoplication.

Appendix S2. Automated impedance manometry analysis data of postoperative EGJ pressures by fundoplication type.

Appendix S3. Conventional impedance data analysis by fundoplication type.

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5.3 SUPPLEMENTARY DATA

Esophageal luminal pressures using conventional analysis before and after fundoplication.

Variable	Liquid bolus N = 19		P- value	Viscous bolus N = 19		P- value
PEAK ESOPHAGEAL PERISTALTIC PRESSURE - level above EGJ, mmHg	*Pre-Op*	*Post-Op*		*Pre-Op*	*Post-Op*	
at 20 cm	50 ± 8	39 ± 5	0.19	33 (26, 64)	33 (22, 58)	0.28
at 15 cm	48 ± 4	59 ± 7	0.12	47 ± 4	53 ± 6	0.35
at 10 cm	74 ± 9	77 ± 10	0.67	56 ± 6	71 ± 8	**0.03**
at 5 cm	74 ± 10	69 ± 9	0.69	54 (39, 102)	53 (38, 78)	0.28
IBP maximum, mmHg	10 ± 2	14 ± 2	**<0.01**	9 ± 1	16 ± 2	**0.02**
EGJ during swallowing	*Pre-Op*	*Post-Op*		*Pre-Op*	*Post-Op*	
Nadir EGJ pressure, mmHg	0.1(0.1,0.6)	4 (0.2, 9)	**<0.01**	0 (-0.5, 0.4)	4 (0.3, 12)	**0.0003**
EGJ during rest period	*Pre-Op*	*Post-Op*				
Basal EGJ pressure, mmHg	3 (0.8, 4.5)	8 (4, 17)	**0.010**			

IBP, intra-bolus pressure; EGJ, esophago-gastric junction. Paired data before and after surgery were

compared using Wilcoxon signed-ranks test or paired t-test.

SUPPLEMENTARY DATA

Automated impedance manometry (AIM) data analysis of post-operative EGJ pressures by fundoplication type.

Variable	Post Op Liquid Bolus N = 19		P-value	Post Op Viscous Bolus N = 19		P-value
EGJ:	*Partial 90° wrap*	*Total 360° wrap*		*Partial 90° wrap*	*Total 360° wrap*	
Basal EGJ pressure, mmHg	11 (5, 17)	23 (20, 60)	**<0.01**	9 (7, 20)	21 (18, 62)	**0.01**
4 sec IRP, mmHg	0 (-1, 3)	14 (8, 24)	**0.001**	2 ± 1.6	19 ± 5.0	**<0.01**

EGJ, esophago-gastric junction; IRP, integrated relaxation pressure.

Data were compared using Mann-Whitney test or t-test.

SUPPLEMENTARY DATA

Conventional impedance data analysis by fundoplication type.

Partial 90° fundoplication N = 11	Liquid bolus		P value	Viscous bolus		P value
Bolus presence time, s	*Pre-Op*	*Post-Op*		*Pre-Op*	*Post-Op*	
at 20 cm	2.2 ± 0.4	4.2 ± 0.7	**<0.01**	2.7 ± 0.6	3.5 ± 0.7	0.42
at 15 cm	3.1 (1.9 – 4.2)	5.8 (3.9 – 6.5)	**0.03**	3.5 ± 0.6	5.1 ± 1.1	0.18
at 10 cm	4.4 (3.7 – 4.5)	6.1 (4.3 – 7.8)	**0.04**	4.9 ± 0.9	5.2 ± 1.1	0.68
at 5cm	5.6 (4.8 – 6.3)	6.3 (6.0 – 8.7)	**<0.02**	5.4 (3.4 – 8.9)	5.4 (3.0-13.5)	0.12
Total bolus transit time, s	5.9 (5.1 – 6.6)	8.1 (6.7 – 9.6)	**<0.02**	8.5 ± 0.8	10.7 ± 1.7	0.17

Total 360° fundoplication N = 8	Liquid bolus		P value	Viscous bolus		P value
Bolus presence time, s	*Pre-Op*	*Post-Op*		*Pre-Op*	*Post-Op*	
at 20 cm	2.1 (1.9 – 2.6))	2.6 (1.7 – 3.1)	0.58	2.0 ± 0.5	3.9 ± 1.0	**0.04**
at 15 cm	2.6 (2.2 – 3.7)	3.8 (3.4 – 5.3)	**<0.02**	3.3 (2.7 – 4.3)	4.8 (3.0 – 8.4)	0.19
at 10 cm	3.6 ± 0.3	5.8 ± 0.6	**<0.02**	3.8 ± 0.5	8.6 ± 1.9	**0.03**
at 5cm	4.4 (4.0 – 5.1)	7.4 (5.4–10.3)	**<0.02**	4.9 (3.1 – 4.4)	9.4 (4.3-14.5)	**<0.02**
Total bolus transit time, s	5.2 (4.4 – 5.4)	7.8 (7.3–11.4)	**<0.02**	5.9 ± 0.7	12.1 ± 1.9	0.06

Bolus presence time for paired impedance rings at a distance above EGJ, esophago-gastric junction. Paired data before and after surgery were compared using Wilcoxon signed-ranks test or paired t-test.

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6

ABERRANT OESOPHAGO-GASTRIC JUNCTION RADIAL PRESSURES ARE ASSOCIATED WITH TROUBLESOME POST FUNDOPLICATION DYSPHAGIA

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By signing the Statement of Authorship, each author certifies that:
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6.2   KEY MESSAGES

- Dysphagia after antireflux surgery remains a significant, unpredictable and poorly understood problem despite empirical modifications to surgical technique.

- Asymmetry of radial oesophago-gastric junction (OGJ) pressure was greater in patients with new-onset troublesome dysphagia after surgery.

- Higher levels of diaphragmatic crural compression associated with hiatal repair best explain this greater asymmetry of OGJ pressure.

- Greater attention to the technical elements of surgery that may cause a higher degree of asymmetrical compression of the OGJ, including the mechanical effects of hiatal repair, may reduce the risk of dysphagia after antireflux surgery.

6.2 ABSTRACT

Background: Radial patterns of oesophago-gastric junction (OGJ) pressure are informative about OGJ mechanics and anatomy. We determined for the first time, the effects of antireflux surgery on OGJ radial pressure patterns and their relationship to post-surgical dysphagia.

Methods: Before and 6 months after surgery, end-expiratory and peak-inspiratory OGJ pressures were measured with 8 radial side-holes at 45° separation in 34 patients with reflux disease. Development of new or worsened troublesome dysphagia (T_Dysph) was assessed by validated questionnaire. All patients underwent crural repair, then 90° anterior (n=13) or 360° (n=21) fundoplication.

Key Results: After 90° fundoplication, end-expiratory OGJ pressures were highest left-anterolaterally corresponding to the position of the partial fundoplication, while in other sectors pressures were uniformly elevated compared to before surgery. Compared to 90° fundoplication, 360° radial OGJ pressures were significantly higher circumferentially (mean p= 0.004), with greatest pressure posteriorly. Comparisons according to dysphagia status showed that the T_Dysph patients had a significantly greater surgery-associated increase in end-expiratory and peak-inspiratory OGJ pressures (p=0.03, p=0.03), and significantly higher inspiratory pressure at the point of maximum radial asymmetry (p=0.048).

Conclusion & Inferences: Circumferential elevation of end-expiratory OGJ pressure after 90° fundoplication suggests hiatal repair elevates OGJ pressure through extrinsic compression. Fundoplication type has distinctive effects on radial OGJ pressure patterns. The localised greater inspiratory OGJ pressure in patients with T_Dysph after fundoplication is best explained by a restrictive diaphragmatic hiatus. These data suggest hiatal repair contributes to post-fundoplication dysphagia. Closer attention to elements of surgery that cause a high degree of asymmetrical compression of the OGJ is warranted.

6.3 INTRODUCTION

Dysphagia is the most troubling adverse effect of antireflux surgery (Humphries *et al.* 2013; Fuchs *et al.* 2014). Alterations of surgical technique to reduce dysphagia risk have been guided more by theory than by measurement of the mechanical factors that cause post-surgical dysphagia (Catarci *et al.* 2004; Watson 2004). Insights from direct observations are limited. A systematic review found that in 43% of patients undergoing revisional surgery for dysphagia, no anatomical abnormality of the antireflux structures was identified at operative inspection (Furnee *et al.* 2009).

Why troublesome dysphagia occurs in some patients after antireflux surgery and not others is a complete enigma (Wills & Hunt 2001). Undoubtedly, dysphagia has a multi-factorial, complex pathogenesis. Some contributing factors have been identified. Patients are at greater risk of post-operative dysphagia if they: (i) report pre-operative dysphagia (Montenovo *et al.* 2009); (ii) have a subtle, pre-existing oesophageal 'pressure-flow mismatch' before surgery (Myers *et al.* 2012b); or (iii) show sub-optimal modulation of oesophageal response to OGJ resistance to outflow (Kwiatek *et al.* 2010; Myers *et al.* 2012a). Failure of this adaptive response to overcome an increased OGJ resistance to outflow after surgery may give rise to dysphagia, as supported by recent studies that show an abnormal response to 'challenge swallows' (multiple rapid swallows) is associated with post-operative dysphagia (Stoikes *et al.* 2012; Wang *et al.* 2015).

The factors that uncover sub-optimal function and modulation of the oesophagus in patients with post-operative dysphagia undoubtedly relate to surgery-induced alterations of OGJ mechanics. Antireflux surgery elevates manometric measures of the resistance of the OGJ to oesophageal emptying, namely distal oesophageal intrabolus pressure (IBP) and residual OGJ relaxation pressure, which is also measured as integrated relaxation pressure (IRP). Additionally OGJ diameter and compliance are reduced following surgery (Pandolfino *et al.* 2005). Yet these measures of OGJ resistance to oesophageal outflow are abnormally elevated in some but not all

patients with post-operative troublesome dysphagia (T_Dysph) (Mathew *et al.* 1997; Anderson *et al.* 1998; Scheffer *et al.* 2005; Marjoux *et al.* 2012). Other aspects of OGJ mechanics are worthy of exploration with regard to T_Dysph, namely radial OGJ pressure patterns and the relative contributions of hiatal repair and fundoplication to altered OGJ mechanics.

Radial or three-dimensional OGJ pressure recordings are rare, yet this measurement approach with either water-perfused manometry or high-resolution radial and axial sensors has shown substantial differences in basal OGJ radial pressures in healthy subjects compared to patients with reflux disease or after antireflux surgery (Winans 1977; Bombeck *et al.* 1987; Stein *et al.* 1995; Kahrilas *et al.* 2000; Nicodeme *et al.* 2013). We have not found any studies that evaluate radial OGJ pressure patterns in patients with T_Dysph after antireflux surgery.

Fundoplication and hiatal repair are essential to achieve the principles of antireflux surgery (Seely *et al.* 2005), however views vary on their relative contributions to T_Dysph (Watson *et al.* 2001; Granderath *et al.* 2005; Bradley *et al.* 2015). The literature is devoid of studies that explore hiatal mechanics before and after antireflux surgery in relation to dysphagia status, which can be assessed by measuring radial OGJ pressure during inspiration and expiration (Kahrilas & Peters 2012).

This prospective study was designed to test the hypothesis that the features of altered OGJ mechanics attributable to fundoplication and hiatal repair are detectable by measurement of radial OGJ pressure patterns at end-expiration or peak-inspiration during regular respiration. We proposed that these measures might differentiate patients with and without T_Dysph. A purpose-designed manometric protocol was carried out before and 6 months after surgery, in conjunction with objective data on dysphagia obtained from a validated self-reporting dysphagia questionnaire.

6.4 METHODS

Subjects

Patients with reflux disease proven by endoscopic mucosal breaks and/ or abnormal 24 h pH monitoring (oesphageal acid exposure time greater than 4%) were invited to participate in this prospective study. Dichotomous (yes/no) questions and visual analogue scales (VAS) were used to document the presence and frequency of heartburn and regurgitation (0 none, 10 frequent). Endoscopy and barium swallow reports documented the size and type of hiatus hernia. Subjects were excluded if they had: a large hiatus hernia (>5cm); a primary motility disorder such as achalasia; an absence of peristalsis such as scleroderma oesophagus; or previous antireflux surgery. The Human Research Ethics Committee, Royal Adelaide Hospital, approved the protocol (#990614a) and all subjects gave written informed consent.

Dysphagia

Before and 6 months after surgery, patients completed a validated dysphagia questionnaire to score the difficulty with swallowing nine different food types of increasing viscosity and solidity, from water to meat (scale 0 -45, 0 = none). This self-reported dysphagia assessment allows for the variable nature of dysphagia by incorporating frequency (never; sometimes; always) along with a patient's experience of dysphagia to solids and liquids, with proven correlation with the ability to swallow these foods (Dakkak & Bennett 1992). Post-operative troublesome dysphagia (T_Dysph) was defined as a dysphagia score that was ≥ 5 above the pre-operative score.

Manometric measurements

Proton pump inhibitors were ceased 5 days prior to testing. Subjects were studied supine after a 6-hr fast, before and 6 months after antireflux surgery, with two types of manometric catheters used sequentially.

<u>Routine oesophageal manometry</u> was performed with an 8-channel oesophageal catheter inclusive of a 6cm sleeve (A-E27-LOSS-1, 3.5mm $\varnothing$, Dentsleeve International, Mississauga, ON Canada). Oesophageal body and lower oesophageal sphincter (LOS) motor function were evaluated during a 5 min rest period, followed by ten, 5 mL water swallows each 30 s apart.

<u>Oesophago-gastric junction axial and radial pressure profiles</u> were recorded with a custom built manometric catheter consisting of 8 side-holes located at the same axial level, of 45° radial separation. A black line, between 45 - 55 cm from the catheter tip, facilitated maintenance of the radial orientation of the catheter at the nostril. Five minutes after catheter insertion, patients were instructed to maintain regular respiration and to cease swallowing during a step-wise, 1-cm station pull-through of the catheter (three times; triplicate data). The catheter was held in the same radial orientation for each station measurement, for at least 3 respiratory cycles from ≥3 cm below the OGJ to ≥3 cm above the OGJ. If a patient inadvertently swallowed, the catheter was held in position until pressures stabilised.

Catheters were perfused with degassed, distilled water using a low compliance perfusion pump. Pressures were detected with external pressure transducers (Abbott Laboratories Ltd, Dublin, Ireland), then digitized at 40 Hz and recorded with Gastromac software (v3.3.5.3, Neomedix Systems Pty Ltd, Sydney, Australia).

Laparoscopic fundoplication

Informed patient preference (see discussion) determined the type of laparoscopic fundoplication undertaken, either an anterior 90° partial or a 360° fundoplication. For both procedures, the oesophageal hiatus was routinely repaired with posterior sutures, so that the oesophagus was lying without compression in the repaired orifice. For a 360° fundoplication, this was confirmed when a bougie was passed through the oesophagus and hiatus without tension. Then a loose 2-cm-long wrap was created over a 52 Fr. intra-oesophageal bougie, with no division of the short gastric vessels, to form a tension-free fundoplication. Great care was taken to mobilise and

position the fundus so that the fundoplication was created with no tension. The middle of three plication stitches was placed through full-thickness fundus and oesophagus to prevent slippage and distortion. The 360° fundoplication was not sutured to the hiatus (Jamieson *et al.* 1994).

The anterior 90° fundoplication involved posterior oesophagopexy to the right hiatal pillar for fixation of a length of oesophagus within the abdomen, re-creation of the angle of His, and creation of a partial fundoplication over the left anterolateral intra-abdominal oesophagus. In particular, for 90° fundoplication formed after the hiatal repair, two sutures secured the fundus to the left side of the oesophagus, then a third apical stitch was placed through full-thickness fundus, oesophagus and the apex of the hiatus. At the 12 o'clock position, a fourth suture was placed distal to the apical stitch, through full-thickness fundus and oesophagus to complete the 90° fundoplication (Krysztopik *et al.* 2002).

A standardised barium swallow was performed at 6 months after surgery to document the post-surgical anatomy of the OGJ region and to evaluate both antegrade and retrograde flow of barium though the oesophagus and OGJ.

Data analysis

Routine diagnostic oesophageal manometry data were analysed in the standard manner. Radial OGJ pressures for each of the three sets of data per subject were determined with software tools for end-expiration and peak-inspiration pressure, for each of the eight radial side-holes for every level of the 1-cm intervals of station pull-through. To facilitate three-dimensional (3-D) plotting, these pressures were referenced to end-expiratory oesophageal baselines. The lower border of the OGJ was defined as the axial level at which intraluminal pressure rose above gastric pressure; and the upper border of the OGJ was defined as the level at which luminal pressure dropped to oesophageal baseline (Swift *et al.* 2001). Triplicate data were averaged for each station pull-through for each subject. For each patient, their pre-operative pressures were subtracted from their post-operative pressures to determine the change in luminal pressures

attributable to antireflux surgery.   Radial pressures were plotted in three-dimensions within MATLAB (version 8.5.0.197613 R2015a, MathWorks Inc., Natick, MA, USA) using data interpolation.

Asymmetry of OGJ pressure was expressed in two ways: a) the difference between maximum and minimum radial pressure, in mmHg; b) degree of asymmetry was expressed as a percentage, %A, such that 100% indicated complete asymmetry and 0% symmetry (i.e. circle)(Kahrilas *et al.* 2000; Swift *et al.* 2001): {1- (min P/ max P)} x 100 = %A. The pressure vector volume of the OGJ, or LOS when a hiatus hernia was present, was calculated for an irregular polygon using simple calculus (Bombeck *et al.* 1987).

Statistical methods

Descriptive statistics include mean ± SEM for parametric and median & interquartile range (IQR) for non-parametric data (SigmaPlot v12, Systat software Inc, San Jose, CA, USA). Data before and after surgery were compared using a paired t-test or Wilcoxon signed-ranks test. Unpaired data comparisons were by either a t-test or Mann-Whitney Rank sum test. Contingency data tables were tested by Fisher's exact or Chi-squared test. Data for patients grouped by dysphagia status and operation type were compared using analysis of variance and statistical differences were evaluated using multiple comparison post-hoc analysis, either Dunn's method or Holm-Sidak method. Statistical significance was accepted for p values < 0.05.

6.5 RESULTS

Forty patients consented to the study, however four patients were excluded because of either an adynamic or scleroderma-like oesophagus (N=3); or a hyperdynamic oesophagus (N =1). A further two patients declined post-operative testing, so our data are derived from 34 patients. Patients reported classical reflux symptoms including heartburn (97%) and regurgitation (100%) over a period of 11.7 ± 1.9 years. All patients used proton pump inhibitors (3.3 ± 0.6 years). Table 6.1 and Supplementary Table 6-S1 list patient characteristics. Oesophageal mucosal breaks were documented in 79% of patients and the remainder had abnormal acid reflux on 24h pH testing (Table 6.1).

Dysphagia Before and After Fundoplication

Table 6.1 and Figure 6.1 give data for dysphagia before and after surgery. Prior to surgery, 4 patients recorded occasional dysphagia for one food type and 8 patients recorded dysphagia for more than one food type.

Assessment 6 months after surgery, found T_Dysph experienced by 6/21 and 3/13 patients for 360° and 90° fundoplication respectively. These patients experienced mild to moderate dysphagia with several food types often on a daily basis compared to those without T_Dysph (score 17, IQR 8, 22.5 vs. 1.5 IQR 0, 4; p < 0.001).

Barium Swallow After Fundoplication

At 6-month post-operative assessment, a barium swallow conducted on the same day shortly after manometry, showed in all cases an intact fundoplication located below the diaphragm and none of the patients demonstrated anatomic abnormalities at the level of the fundoplication such as herniation or dislocation. In 25 patients free of T_Dysph, barium flowed freely through the oesophagus and the OGJ, although two patients showed slow oesophageal stripping waves (known pre-existing hypodynamic oesophagus). Of 9 patients with T_Dypsh, two patients had

slow oesophageal outflow and mild retrograde flow of barium (360° fundoplication); one patient was found to have a narrow OGJ canal with good outflow (360° fundoplication); and only one patient demonstrated hold-up of barium in the distal oesophagus above the OGJ. For the latter patient, an endoscopic dilation was performed at 15 months after 90° fundoplication, with good relief of dysphagia symptoms. No patient underwent revisional surgery for dysphagia.

Overall Radial pressure profile of OGJ prior to surgery

Pre-operatively, in patients negative for hiatus hernia on imaging, there was a single OGJ high-pressure zone, with an almost uniform end-expiratory radial profile of low pressure (asymmetry 16%, Figure 6.2a). At the peak of the inspiratory OGJ pressure rise, the OGJ pressure became substantially asymmetric, with the left-anterolateral pressure being highest (asymmetry 42%, Figure 6.2b).

In 14 patients with hiatus hernia, diagnosed by imaging (range 1-5 cm, mean 3.2 cm), there were two high-pressure zones (Figure 6.2c & 6.2d). The proximal high-pressure zone, attributed to the LOS, exhibited low and asymmetrical pressure during end-expiration and peak inspiration (asymmetry 44%, 56% respectively). The distal high-pressure zone, attributed to the crural diaphragm was virtually symmetrical at end-expiration and peak-inspiration (asymmetry 14%, 14% respectively; Figure 6.2c & 6.2d). A further two patients diagnosed with a hiatus hernia during endoscopy (1cm; 5cm) were negative for hiatus hernia during manometry.

At the level of the crural diaphragm, peak inspiratory OGJ pressure was substantially lower in patients with, compared to those without, a hiatus hernia (26 mmHg IQR 23,31 vs. 42 mmHg IQR 28,51; p= 0.0006, Figure 6.2).

Overall Radial pressure profile of OGJ after fundoplication

Following surgery, all patients had a single OGJ high-pressure zone and post-operative OGJ radial pressures were greater than before surgery. Plots of OGJ pressures show that the

magnitude, and the axial and radial orientation of pressures differed for the two types of fundoplication (Figure 6.3). After a 90° fundoplication, there was circumferential elevation of luminal OGJ pressure compared with pressures before surgery. End-expiratory OGJ pressure was consistently highest in the left-anterolateral quadrant, corresponding to the position of the partial fundal wrap. After 360° fundoplication, end-expiratory pressure was circumferentially elevated, but in contrast to 90° fundoplication, radial pressures were consistently highest in the posterior sectors (Figure 6.3). Group mean radial pressure at the level of the highest axial end-expiratory OGJ pressure was greater following 360° compared to 90° fundoplication (p= 0.004), with similar findings for maximum and minimum radial pressure (Table 6.2).

Inspiratory pressures were also informative. Compared to 90° fundoplication, patients evaluated after 360° fundoplication showed greater OGJ pressure increase with inspiration (p=0.01). At the level of the highest axial OGJ pressure, the minimum radial pressure was significantly greater following 360° compared to 90° fundoplication during both expiration and inspiration (Table 6.2; Figure 6.3).

OGJ pressure vector volume and axial length of the OGJ high-pressure zone were significantly greater following 360° compared to 90° fundoplication (Supplementary Table 6-S2).

Post-operative Dysphagia and OGJ mechanics

In the 9 patients with T_Dysph after fundoplication (3x 90°; 6x 360°) the net increase in peak-inspiratory OGJ pressure after surgery was higher (p=0.048), compared to the patients without T_Dysph (n=25). After surgery, the net increase in maximal end-expiratory OGJ pressure though numerically higher in patients with T_Dysph compared to those without, did not reach statistical significance (p = 0.06; Table 6.3). For patients with T_Dysph, compared to those without, the degree of radial asymmetry of OGJ pressure was significantly greater for end-expiratory and peak-inspiratory pressure (p = 0.03, p = 0.03 respectively, Table 6.3, Figure 6.4). The orientation of focal high OGJ pressure was in the posterior and left-posterolateral sectors for 5/6 with

T_Dysph after 360° fundoplication, and in the left-lateral and left-anterolateral sectors for 3/3 patients with T_Dysph after 90° fundoplication. OGJ pressure vector volume did not differentiate patients with T_Dysph from patients without (p=0.16, Supplementary Table 6-S2).

Routine manometric findings

Prior to surgery, routine pre-operative manometry revealed a hypotensive OGJ (median 4 mmHg, IQR 2,9), and intact primary peristalsis (100%, IQR 90,100). These parameters did not differ significantly between those who subsequently received a 90° or 360° fundoplication, but sleeve OGJ resting pressure and distal contractile amplitude were significantly lower in patients with than without hiatal hernia (Supplementary Table 6-S3). Dysphagia before surgery was not associated with the presence of a hiatus hernia (p= 0.69, Fisher's Exact test).

Post-operatively, routine manometry showed a normotensive OGJ (median 19 mmHg, IQR 12, 23) and intact primary peristalsis (100%, IQR 74, 100). Post-surgical measurements of peristalsis and contraction amplitude were not significantly different between patients with or without T_Dysph. Sleeve OGJ resting and residual relaxation pressure were significantly higher after 360° compared to 90° fundoplication (p = 0.002; p< 0.001 respectively), but did not differ significantly for patients with or without T_Dysph (p = 0.61; p = 0.15 respectively; Supplementary Table 6-S3).
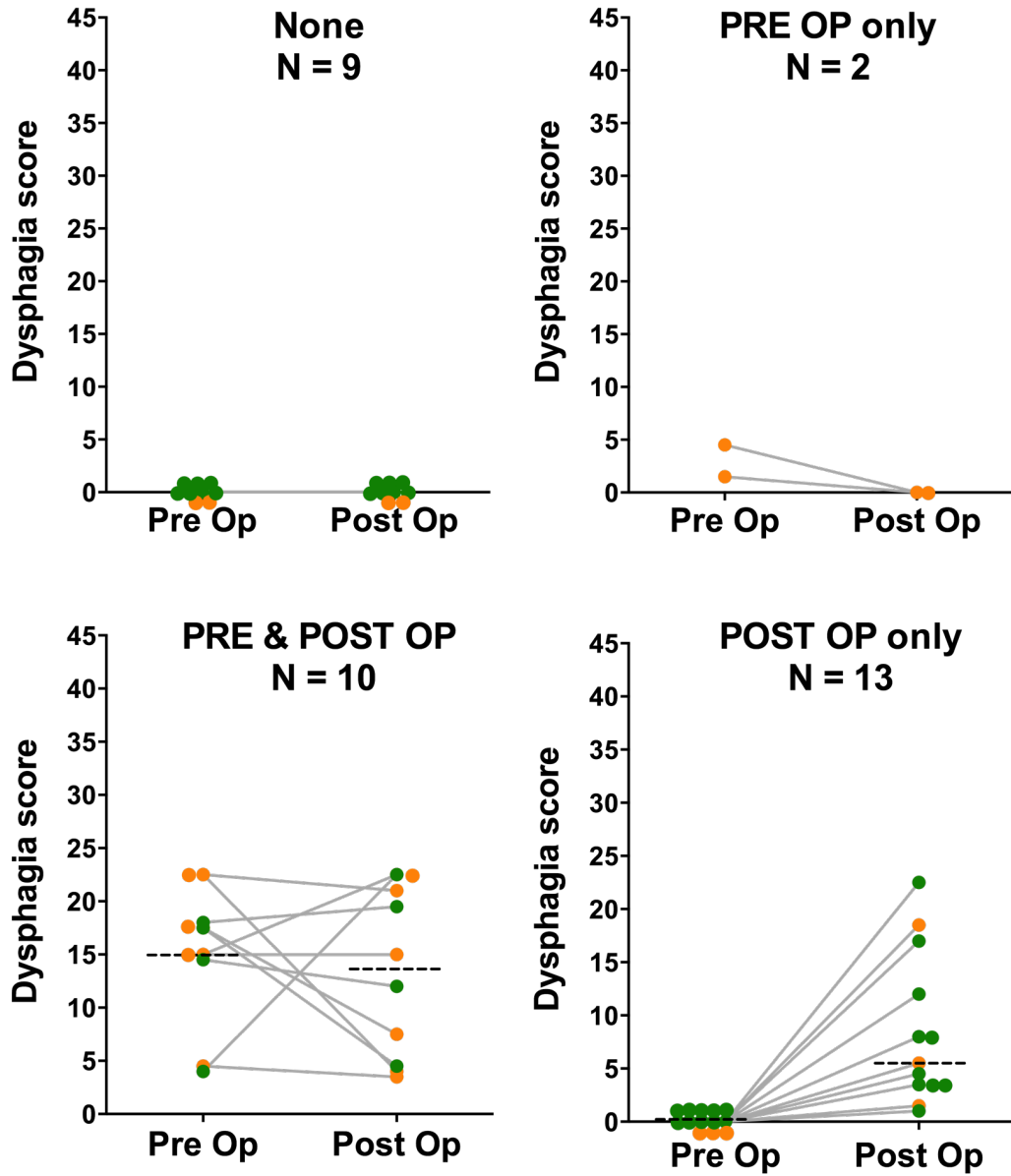
Figure 6.1   Dysphagia scores for difficulty with swallowing 9 food types according to four

patterns of dysphagia presentation before and after surgery
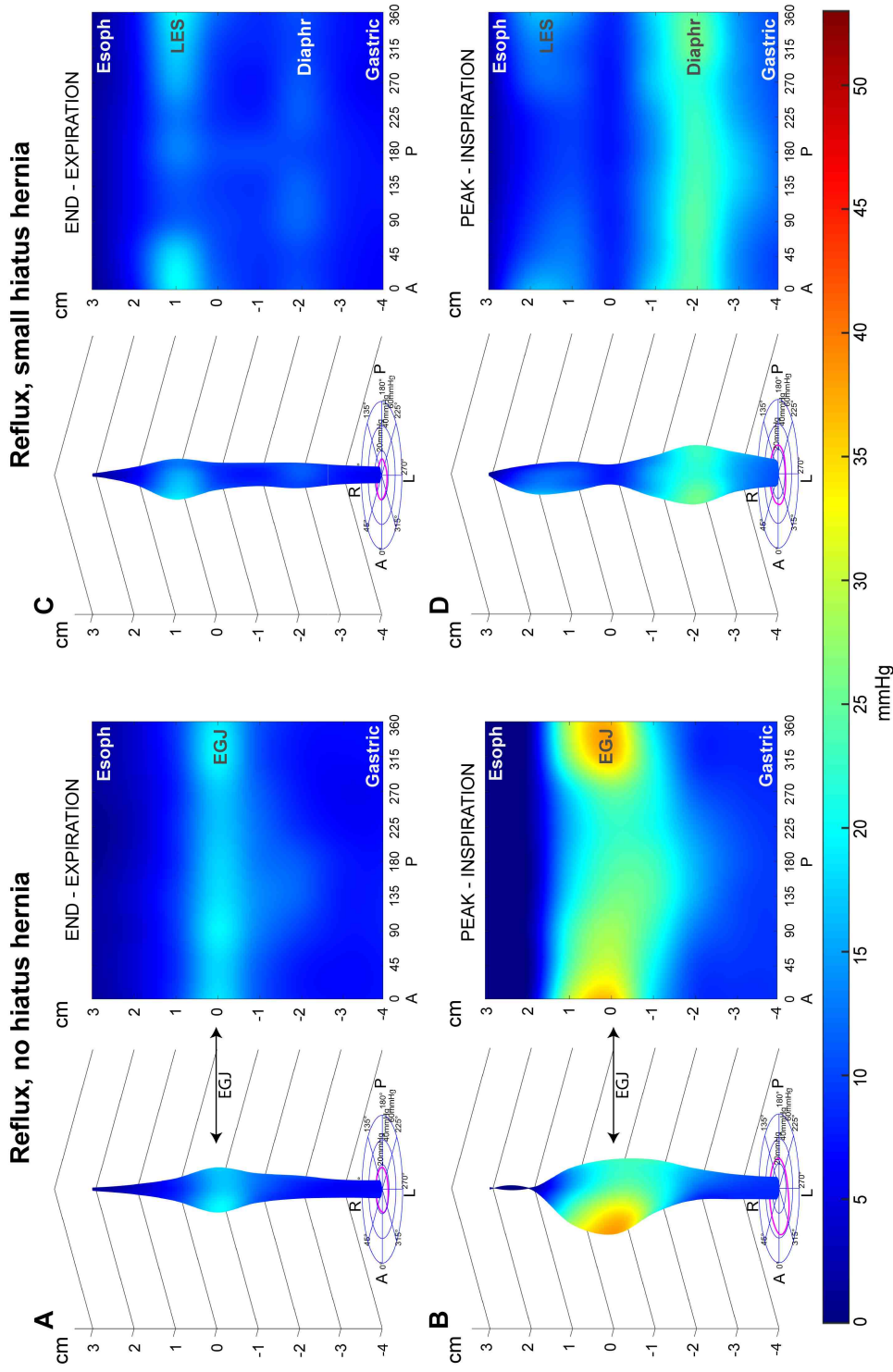
(● = 90° fundoplication; ● = 360° fundoplication).

Figure 6.2. **End–expiratory and peak–inspiratory EGJ radial pressure for the patient population prior to fundoplication, according to the presence (N=14) or absence (N=20) of a hiatus hernia.** The purple oval at the base of each 3-D plot displays the radial profile at the level of the highest radial pressure. To the right of each 3-D plot, is the 2-D plot of the same data. Plot orientation: A, anterior $0°$, P, posterior $180°$.
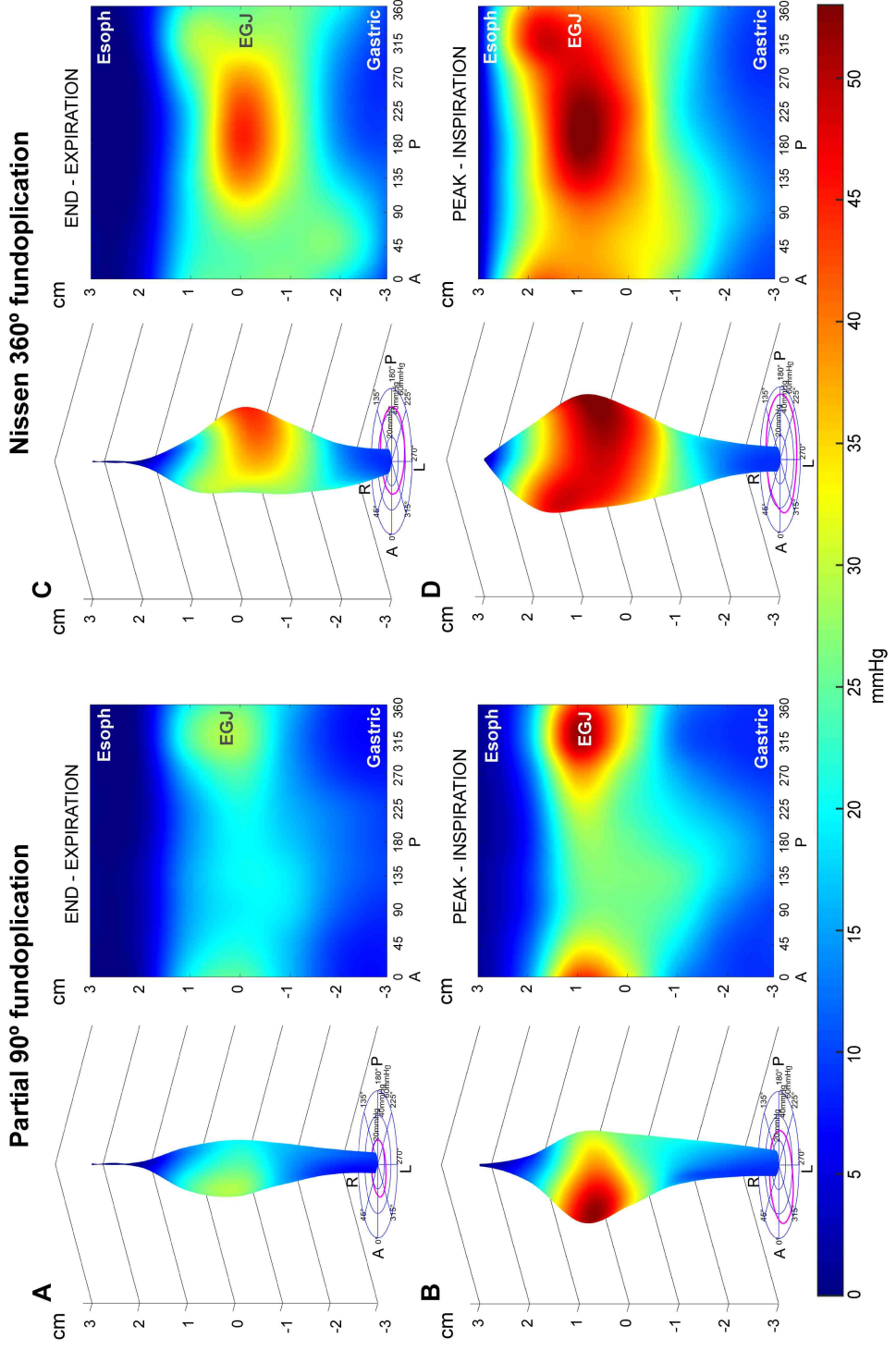
Figure 6.3. End-expiratory and peak-inspiratory EGJ radial pressure following 90° fundoplication (N=13) and 360° fundoplication (N=21). See Figure 2 legend for other explanatory details.

With significant dysphagia

Without significant dysphagia
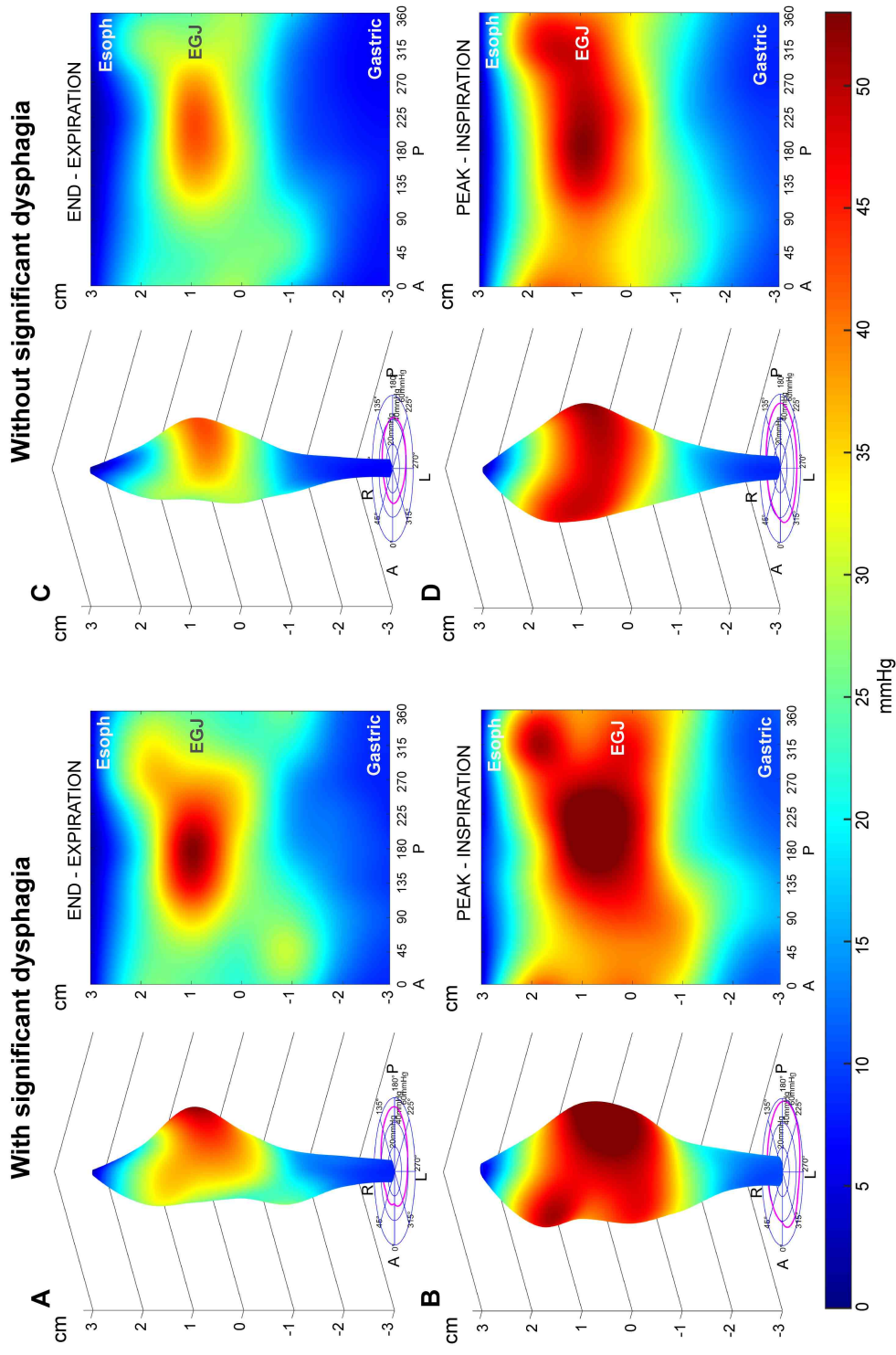
Figure 6.4. End-expiratory and peak-inspiratory EGJ radial pressure in patients after 360° fundoplication according to the presence (N=6) or absence (N=15) of troublesome dysphagia. See Figure 2 legend for other explanatory details.

TABLE 6.1: Patient demographics, reflux disease assessments and symptoms scores

Before Surgery	Anterior 90° fundoplication N = 13	Nissen 360° fundoplication N = 21	P value
Age[a], years	53.2 (30 – 77)	43.7 (23 – 69)	0.07
Gender, M: F	2M : 11F	19M : 2F	<0.001
BMI[b], kg/m^2	26.2 ± 1.2	30.6 ± 0.9	0.006
Endoscopy findings:			
Normal	2	5	
Oesophagitis	9	10	0.46
Barrett's oesophagus	2	6	
Hiatus hernia +, N (%)	6 (18%)	8 (24%)	
Hiatus hernia - , N (%)	7 (21%)	13 (38%)	0.73
24h pH monitoring	N = 9	N = 18	
Acid Exposure % [b]	12.0 ± 2.8 %	12.1 ± 1.7 %	0.97
# Acid reflux events [b]	64 ± 9	67 ± 7	0.84
Heartburn, VAS score	8 (5, 10)	9 (7.5, 10)	0.46
Regurgitation, VAS score	6 ± 0.9	6 ± 0.7	0.85
Dysphagia score[c]	4 (0, 16)	0 (0, 0)	0.02
After Surgery			
Heartburn, VAS	0 (0, 7)	0 (0, 0)	0.02
Regurgitation, VAS	1 (0, 2)	0 (0, 1)	0.2
Dysphagia score[c]	4 (0, 17)	3.5 (0,12)	0.8

[a] Data are mean (range), [b] Data are mean (± SEM), [c] Data are median (Q1, Q3)
VAS, visual analogue scale

TABLE 6.2: OGJ pressure characteristics for operation type

Operation type Pressure, mmHg	Anterior 90° fundoplication N = 13	Nissen 360° fundoplication N = 21	P value
End-Expiratory OGJ Pressure			
Mean of 8 x radial pressure	23 ± 2.5	35 ± 2.6	0.004
Maximum, 8 x radial pressure	33 (25, 48)	41 (36, 66)	0.03
Minimum, 8 x radial pressure	17 ± 2.5	24 ± 1.3)	0.01
Differential, maximum-minimum	17 (13, 23)	18 (14, 42)	0.60
Peak-Inspiratory OGJ Pressure			
Mean of 8 x radial pressure	31 (24, 43)	45 (38, 54)	0.01
Maximum, 8 x radial pressure	56 (41, 67)	64 (52, 83)	0.12
Minimum, 8 x radial pressure	23 (12, 30)	29 (25, 36)	0.03
Differential, maximum-minimum	29 (21, 47)	33 (23, 45)	0.67

Data are mean (± SEM) or median (Q1, Q3). Data analysis by t-test or Mann-Whitney Rank Sum test.

TABLE 6.3: **OGJ pressure characteristics for dysphagia status after surgery**

Surgery-related OGJ pressure change Pressure, mmHg	Patients without T_Dysph N = 25	Patients with T_Dysph N = 9	P value
End-Expiratory Post-op OGJ minus Pre-Op LOS pressure			
Mean of 8 x radial pressure	12 ± 2.3	17 ± 4.4	0.32
Maximum, 8 x radial pressure	26 ± 3.7	41 ± 7.4	0.06
Minimum, 8 x radial pressure	2 (-9, 7)	3 (-9, 9)	0.91
Differential, maximum-minimum	21 (15, 32)	38 (30, 42)	0.03
Peak-Inspiratory Post-op OGJ minus Pre-Op LOS pressure			
Mean of 8 x radial pressure	14 ± 2.7	23 ± 7.6	0.17
Maximum, 8 x radial pressure	32 ± 4.5	54 ± 13.2	0.048
Minimum, 8 x radial pressure	2 (-7, 6)2	-6 (-12, 15)	0.69
Differential, maximum-minimum	29 (18, 42)	44 (36, 90)	0.03

Data are mean (± SEM) or median (Q1, Q3). Data analysis by t-test or Mann-Whitney Rank Sum test.

6.6 DISCUSSION

The important findings of this study are firstly, that a radially limited fundoplication (90°) with hiatal repair imposes circumferential extrinsic compression of the OGJ. Secondly, the radial OGJ pressure patterns are strikingly different for anterior 90° fundoplication and 360° fundoplication. The third major and most important finding is that troublesome dysphagia, attributable to antireflux surgery, was associated with a high degree of asymmetrical compression of the OGJ.

It is important to note that this study evaluated consecutive consenting patients who underwent primary surgery in a tertiary centre specialising in laparoscopic antireflux surgery. All patients were evaluated comprehensively at 6-months after surgery, when all were found to have an intact, sub-diaphragmatic fundoplication on fluoroscopy with no anatomical abnormality, and a single high-pressure zone associated with the antireflux barrier on manometry. A small sub-group of patients (9/34, 26%) reported having mild to moderate dysphagia. We have labelled this as 'troublesome dysphagia', because it was severe enough to be annoying or bothersome. No patient reported having severe dysphagia and none required revisional surgery, though one had a dilatation. This pattern of dysphagia severity is in keeping with other published data. Dysphagia is almost universally experienced in the early post-operative period (93%, < 6 weeks) (Funch-Jensen & Jacobsen 2007) and lessens with the passage of time to plateau at about 30% at 6 months after surgery (O'Boyle *et al.* 2002).

The circumferential elevation of OGJ pressures after both types of surgery is an intriguing finding. The superimposed contributions of the LOS, the fundoplication and the hiatal repair could hinder interpretation of OGJ pressures. However, findings in the 90° fundoplication patients are especially revealing. The zone of higher end-expiratory OGJ pressure in the left-anterolateral radial sectors is consistent with the mechanical effects of the partial fundal wrap (Figure 6.3). Yet in the other radial sectors there was a relatively uniform elevation of OGJ

pressure above gastric pressure, which was not present prior to surgery. We did not expect this circumferential elevation of OGJ pressure for such a radially limited fundoplication and have concluded that passive extrinsic compression of the OGJ by the repaired hiatus is the best explanation for this finding.

Similarly, a portion of the circumferential elevation of end-expiratory OGJ pressure seen after $360°$ fundoplication is also attributable to passive compression by the repaired hiatus, but cannot be identified separately as the mechanics of this fundoplication type bear on the whole circumference of the OGJ. This interpretation is supported by the intra-operative high-resolution manometry (HRM) study by Louie *et al.*, in which the effects of hiatal repair and fundoplication were assessed separately. Louie *et al.* randomised 18 patients to either hiatal repair first or fundoplication first. 'Hiatal repair first' augmented OGJ pressure by a mean of 10.2 mmHg, whereas for '360° fundoplication first', OGJ pressure rose by a mean of only 3.5 mmHg (p = 0.07) (Louie *et al.* 2013). While the difference in contribution to OGJ pressure by hiatal repair compared with that of fundoplication was not statistically significant, this study shows that hiatal repair alone has a substantial impact on OGJ pressure, a concept that is alien to most thinking about OGJ pressure after antireflux surgery.

Using a different approach, Kahrilas *et al.* came to the same conclusion. Radial OGJ pressures were recorded to determine the contribution of surgery to the radial OGJ pressure profile (Kahrilas *et al.* 2000). The authors subtracted LOS pressures recorded during suspended respiration in 7 un-operated reflux patients with hiatus hernia from the OGJ pressures measured in 7 patients after $360°$ fundoplication, and similarly for hiatal canal pressure. This approach led to the conclusion that there was extrinsic compression of the OGJ by the repaired hiatus after $360°$ fundoplication.

We built on the approach of Kahrilas *et al.* to assess surgery-related OGJ pressure change (Kahrilas *et al.* 2000) by subtracting individual patient pre-operative pressures from their post-

operative pressures. There was significantly greater surgery-associated asymmetry of OGJ pressure in patients with T_Dysph, compared to those without, during end-expiration and peak-inspiration (Table 6.3, Figure 6.4).

The before/ after differential OGJ pressures in Table 6.3 (median and IQR) were significantly different to separate patients with and without T_Dysph. The significantly larger OGJ pressure elevation (Table 6.3) in patients with T_Dysph occurred after both types of fundoplication and in radial sectors where the forces of both hiatal repair and fundoplication were active i.e. posteriorly after 360° fundoplication and left-anterolaterally after 90° fundoplication. The cause of this focal point of high OGJ pressure might be from compression of the OGJ associated with: (i) the fundus and repaired hiatus fitting snugly between adjacent structures (e.g. liver; spine); (ii) a localised narrowing from the repaired hiatus; (iii) a spiralled or twisted fundoplication, or (iv) reduced OGJ compliance in the sector associated with the re-created angle of His.

In the nine patients with T_Dysph, three underwent 90° fundoplication and six underwent 360° fundoplication. Not only are these different types of fundoplication in terms of circumferential extent, but also they have varying concomitant technical elements to achieve the principles of antireflux surgery. For 90° fundoplication, gastropexy and full thickness sutures through the fundus and oesophagus secure the plication (see methods). A spiralled or twisted fundoplication is unlikely to occur in the 90° plication, as there is no rotational effect of anterior suturing. Localised high OGJ pressure in patients with T_Dysph could be due to reduced OGJ compliance associated with the re-created angle of His or the repaired hiatus compressing the OGJ.

For 360° fundoplication, it is conceivable that an abnormal focal compression of the OGJ after 360° fundoplication in patients with T_Dysph occurs posteriorly due to compression of structures (fundus, hiatus) within a confined space. However the greatly accentuated, and axially and radially highly localised, peak-inspiratory pressure suggests a focal point of extrinsic compression of the OGJ, which is best explained by contraction of the diaphragmatic crura. Further studies are

needed to determine if marked inspiratory hiatal squeeze pressure is a signature of a 'snug' hiatus in patients with T_Dysph.

The findings of this present study are consistent with studies that show antireflux surgery raises residual OGJ pressure during swallow-induced relaxation (Dent *et al.* 1982; Kiroff *et al.* 1984; Ireland *et al.* 1993; Mathew *et al.* 1997; Scheffer *et al.* 2004). A focal point of high OGJ pressure is also consistent with studies that show the narrowest width and least distensible part of the OGJ after antireflux surgery is located at the level of the diaphragmatic hiatus (Pandolfino *et al.* 2005; Scheffer *et al.* 2005; Kwiatek *et al.* 2010).

The major strengths of this study are its purpose-designed pre- and post-operative fluoroscopic observations and its measurements of dysphagia and radial OGJ pressures in a well-defined patient group. The comparison of two types of fundoplication enhanced the interpretation of the study data. The inclusion of peak-inspiratory pressures was critical to exploring passive and active hiatal compression effects on the OGJ.

A limitation of this study is the small number of patients with T_Dysph that was mild to moderate, an unforeseeable reality of prospective evaluation of antireflux surgery-related dysphagia. Though we considered formal randomisation of patients to 90° or 360° fundoplication, we deemed this was not justified, as our aim was to evaluate the mechanics of dysphagia, regardless of fundoplication type. The information given to patients to enable them to make an informed choice of operation type included advice that 360° fundoplication provides the most reliable control of reflux, but carries a greater risk for increased flatulence (Varin *et al.* 2009). As previously shown (Myers *et al.* 2012a), this is of particular concern to women and led to the preponderance of women in the 90° fundoplication group.

Further studies are needed to better understand the focal point of high OGJ pressure observed in patients with T_Dysph. Patients with post-surgery dysphagia severe enough to warrant

revisional surgery are the key patient population for such studies. Functional luminal impedance planimetry (EndoFLIP) with measures of luminal cross-sectional area and OGJ distensibility is a promising (albeit radially insensitive) technique for direct assessment of objective data on OGJ luminal diameter and compliance to assess the impacts of hiatal repair and fundoplication on OGJ function (Nathanson *et al.* 2012).

In conclusion, the data from this study suggest that the risk of post-operative dysphagia may be reduced if we can better understand elements of surgery that cause a high degree of asymmetrical compression of the OGJ.

6.7   ACKNOWLEDGEMENTS

6.8   SUPPLEMENTARY DATA

Supplement 6-S1:

Demographic data for reflux patients with and without hiatus hernia.

	no hiatus hernia N = 20	hiatus hernia N = 14	P value
Age[a], years	44.8 (23 – 69)	50.9 (27 – 77)	0.24
Gender, M: F	15M : 5F	6M : 8F	0.08
BMI[b], kg/m^2	27.8 ± 1.0	30.4 ± 1.3	0.11
Endoscopy findings:			
Normal	5	2	} 0.69
Oesophagitis	11	8	
Barrett's oesphagus	4	4	
24h pH monitoring	N = 18	N = 9	
Acid Exposure % [b]	10.9 ± 1.7 %	14.4 ± 2.5 %	0.25
# Acid reflux events [b]	67 ± 8	64 ± 8	0.84
Heartburn, VAS score	8 (7, 10)	9.5 (7, 10)	0.50
Regurgitation, VAS score	5 ± 0.6	7 ± 0.9	0.06
Dysphagia score[c]	0 (0, 4)	0 (0, 16)	0.36

[a] Data are mean (range), [b] Data are mean (± SEM), [c] Data are median (Q1, Q3)

VAS, visual analogue scale

SUPPLEMENTARY DATA

Supplement 6-S2:

OGJ pressure vector volume and OGJ length for operation type and dysphagia status.

A: Operation type Pressure Vector Volume mmHg.mmHg.cm	Anterior 90° fundoplication N = 13	Nissen 360° fundoplication N = 21	P value
Total Vector Volume	4420 (2528, 9928)	14657 (9301, 21754)	<0.001
Vector Volume at level of max OGJ Pressure	1990 (1575, 4673)	6590 (3754, 11007)	0.003
Ave Vector Volume/ cm	1240 (970, 3309)	3544 (2191, 5842)	0.004
Length of OGJ Post Op (max, cm)	3 (3, 4)	4 (4, 5)	0.002

B: Dysphagia status Pressure Vector Volume mmHg.mmHg.cm	Patients without T_Dysph N = 25	Patients with T_Dysph N = 9	P value
Total Vector Volume	9580 (4285, 17231)	14925 (9142, 21931)	0.16
Vector Volume at level of max OGJ Pressure	4415 (1899, 7234)	5186 (3434, 11007)	0.25
Ave Vector Volume/ cm	2578 (1206, 4449)	3731 (2446, 4996)	0.10
Length of OGJ Post Op (max, cm)	4 (3, 4)	4 (3, 4.5)	0.63

Data are median (Q1, Q3). Data analysis by Mann-Whitney Rank Sum test.

SUPPLEMENTARY DATA

Supplement 6-S3:

Routine manometric oesophageal and oesophago-gastric junction measurements.

A: Pre- operative manometry:	no hiatus hernia N = 20	hiatus hernia N = 14	P value
Primary peristalsis, %	100 (90, 100)	100 (73, 100)	0.67
Distal oesophagus amplitude, mmHg*	82 (56, 113)	51 (40, 71)	0.02
Sleeve OGJ resting pressure, mmHg†	7 (3, 12)	2.5 (0, 6)	0.02
Residual relaxation pressure, mmHg†	0 (0, 1)	0 (0, 0)	0.13

B: Post- operative manometry:	Anterior 90° fundoplication N = 13	Nissen 360° fundoplication N = 21	P value
Primary peristalsis, %	90 (50, 100)	100 (80, 100)	0.18
Distal oesophagus amplitude, mmHg*	70 (32, 107)	70 (60, 93)	0.5
Sleeve OGJ resting pressure, mmHg†	11 (7, 20)	21 (17, 34)	0.002
Residual relaxation pressure, mmHg†	3 (1, 4)	7 (4, 10)	<0.001

C: Post-op Dysphagia:	Patients without T_Dysph N = 25	Patients with T_Dysph N = 9	P value
Primary peristalsis, %	100 (69, 100)	80 (65, 95)	0.15
Distal oesophagus amplitude, mmHg*	72 ± 6	75 ± 11	0.82
Sleeve OGJ resting pressure, mmHg†	19 (11, 22)	19 (14, 34)	0.61
Residual relaxation pressure, mmHg†	4 (2, 7)	7 (4, 14)	0.15

*Oesophageal pressure referenced to oesophageal end-expiration baselines. †OGJ resting and residual relaxation pressures referenced to end-expiration gastric baseline.

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7

CONCLUSIONS AND FUTURE DIRECTIONS

7.1 Conclusions

7.1.1 Aim 1

- **To evaluate the mechanism of early post-operative dysphagia. It is often assumed that early post-operative dysphagia after laparoscopic fundoplication is due to oedema. Whether dysphagia is associated with a change in oesophageal motility and/or a change in oesophago-gastric junction characteristics of function is unknown.**

In the first study (Chapter 2), manometry revealed oesophageal ileus in the 24 hours after fundoplication, but not cholecystectomy. This ileus is likely to be an important factor in the pathogenesis of dysphagia so prevalent in the peri-operative period.

The high susceptibility of oesophageal peristaltic mechanisms to the manipulations of antireflux surgery would probably be a surprise to most. Oesophageal ileus has also been noted in a non-surgical setting. Oesophageal ileus was observed following inadvertent triggering of vomiting in 3/13 healthy subjects during induction of acute nausea by caloric labyrinthine stimulation (Cook *et al.* 1993)[6]. This demonstration of a potent inhibition of the oesophageal function by central nervous stimulus emphasises how susceptible oesophageal motor controls are to extraneous influences.

Since publication of the first study (Chapter 2) in 2007, Unden Ozcan *et al.* in Turkey have investigated whether disturbance of the intrinsic nerve supply of the OGJ region during surgery could be the cause of ileus. Following fundoplication in 8 male rats, they found a significant decrease in the number of interstitial cells of Cajal, the intestine pacemaker cells, in the OGJ region. These cells are electrically coupled to smooth muscle cells, so a decrease in these cells may interrupt normal control of the muscles. This could account for the diminished contractility

[6] Bibliography for Chapters 1 & 7 begins on p. 185

of the distal oesophagus, though the investigators did not assess this. More studies are needed to identify the steps of antireflux surgery (dissection, mobilisation and even the silk suturing material), that may induce changes at the cellular level (Unden Ozcan *et al.* 2015).

In the first study, the duration of oesophageal ileus was not determined, but 3 months after surgery, oesophageal body peristalsis was similar to pre-operative findings in all but two patients. A further study is needed to define the time course of ileus.

At 3 months after surgery OGJ residual pressure was less than day-1 after surgery, but greater than before surgery.   Also a number of patients reported troublesome dysphagia despite regaining oesophageal body function. In hindsight, a semi-solid bolus rather than a 5mL water swallow bolus would have been a better stimulus to challenge oesophageal vigour of peristalsis to determine if peristaltic strength was sufficient to overcome the new OGJ antireflux barrier.

This study:

1. Indicates that patient informed consent procedures and peri-operative management should include awareness of the likelihood of oesophageal ileus after day-case and inpatient laparoscopic fundoplication.   Dysphagia (3%) and pain (5%) are the main reasons for readmission after day-case fundoplication (Thomas & Agrawal 2011);

2. Adds weight to caution patients against resuming a normal diet upon discharge and to adhere to a soft food diet and free liquids for 6 weeks after antireflux surgery;

3. Raises the question, do 'next generation' antireflux procedures similarly disturb motility? This is worthy of evaluation. Endoluminal techniques and the Linx™ system could become the next generation of minimally invasive antireflux surgery. There are currently 3 types: EsophyX™ system (EndoGastric Solutions), uses polypropylene 'H shaped' fasteners for a full-thickness plication; the Stretta® system (Mederi Therapeutics Inc), uses radiofrequency energy on OGJ muscle to increase LOS pressure; and the Linx™ system (Torax® Medical Inc)

augments LOS pressure via a ring of magnetic beads (Kim & Velanovich 2014). Their impact on peristalsis in the peri-operative period is unknown.

7.1.2　　　Aim 2

- **To evaluate patients with late persistent dysphagia presenting for revisional surgery to ascertain the findings at surgery and the technical elements revised to treatment this symptom. To assess all patients presenting with symptoms warranting revisional surgery, to compare and contrast the indications for and symptomatic outcomes of late (>6 weeks) revisional surgery.**

The second study (Chapter 3) found the rate of late revisional surgery was 5.6% in our Unit, including 3% for dysphagia. This is similar to a subsequent published review by the EAES panel of experts, who found a re-operation rate of 3 - 6 % (Fuchs *et al.* 2014). In our study, dysphagia, proven recurrent reflux and herniation were the most common indications for revision (48%, 33% 15% respectively). However, which of these is the most common indication for surgical revision varies amongst centres (Richter 2013; Fuchs *et al.* 2014). This is likely due to different operative techniques, patient selection and disease severity.

Shortly after publication of the second study (Chapter 3), a systematic review of revisional antireflux surgery by Furnée *et al.* found intra-thoracic herniation of the wrap into the thoracic cavity was the most common technical failure of primary antireflux surgery (Furnee *et al.* 2009). Herniation can result from inadequate closure of the hiatus or disruption of the crural closure post surgery. Contributing factors might include: excessive mechanical strain on the closure by retching; suboptimal crural muscle architecture, as myofibril and sarcomere degeneration of crura muscle has been found in patients with, but not without, reflux disease (Fei *et al.* 2009); or another possibility is abnormal radial tension on the repaired hiatus. Hiatal tension can be measured intra-operatively with a tensiometer and was found to be significantly higher in patients with a para-oesophageal hernia compared to sliding hernia (Bradley *et al.* 2015). Thus

crural repair to reduce hiatal width may inadvertently increase radial and /or axial tension in the repaired hiatus. In addition, previous hiatal hernia increases the risk for re-herniation via as yet undefined mechanisms (Koch *et al.* 2011). The use of mesh to reinforce the hiatus might reduce recurrence, but is not advocated routinely because of problems with post-operative dysphagia, mesh dislocation and penetration of the mesh through adjacent structures (Fuchs *et al.* 2014).

In our Unit, it was not inadequate hiatal closure, but hiatal narrowing that was a more common finding (Chapter 3). In our 52 patients undergoing revision for dysphagia, 26 patients had a degree of hiatal narrowing requiring widening of the hiatus to rectify either a rigid hiatus with dense fibrosis or an overly narrow hiatal repair. Others have recognised that narrowing the hiatus can contribute to post-surgery dysphagia (Kahrilas *et al.* 1998; Le Blanc-Louvry *et al.* 2000; Granderath *et al.* 2005). In the fifth study (Chapter 6), OGJ 3-D pressure sampling showed a greater asymmetrical compression of the OGJ in patients with but not without troublesome post-operative dysphagia. This focally high OGJ pressure was greatest during inspiration and was interpreted as most likely associated with hiatal repair. To date objective criteria for hiatal repair that might minimise post-operative dysphagia are lacking. Endoscopic functional luminal impedance planimetry (EndoFLIP®), which measures luminal cross-sectional area and EGJ distensibility, and intra-operative measurement of hiatal surface area are two promising techniques for objective calibration of hiatal repair (Granderath *et al.* 2007; Nathanson *et al.* 2012). The use of these techniques and their impact on surgery-related dysphagia in well-designed prospective studies is awaited.

The finding in the second study (Chapter 3) that a refashioning of a tight fundoplication was required in 21% of patients needing surgical revision for dysphagia, implies that the current method of calibrating the fundal wrap over a 52 Fr. bougie does not always create a loose, floppy 360° fundoplication. Supplementary calibration, using EndoFLIP® as a 'smart bougie', is conceivable (Perretta *et al.* 2013). The orientation, position and suturing of a fundal wrap might be adjusted in response to real-time measurements of OGJ luminal cross-sectional area and

compliance. Studies are needed to determine if this approach leads to a reduction in post-operative dysphagia.

Our study of patients undergoing revisional surgery for dysphagia showed that patients with no identifiable abnormality at re-operation obtained some relief of dysphagia by conversion to a partial fundoplication. This implies that an unidentified physiological or mechanical effect of surgery, while not recognised at operative inspection, is altered by such revision. Future studies are needed to explore objective measures of physiological change associated with dysphagia and its surgical relief, because if we can't measure it, we can't control it. This might explain why patients having revisional surgery for dysphagia have lower patient satisfaction with outcome than revisional surgery for recurrent reflux.

7.1.3 Aim 3

- **To explore factors that put a patient at risk of developing dysphagia after antireflux surgery.**

The third and fourth studies, both published in 2012 (Chapters 4 & 5), show that higher OGJ residual relaxation pressure and sub-optimal local intrinsic modulation of oesophageal function in response to altered OGJ function are associated with post-operative dysphagia. Also the circumferential extent of fundoplication influenced significantly both residual OGJ relaxation pressure and distal intrabolus pressure. These measures correlated with dysphagia to solids after antireflux surgery and a pre-operative Dysphagia Risk Index, DRI > 14 predicted development of post-operative dysphagia.

More recent studies using either low- or high-resolution manometry are mostly limited to findings for 360° fundoplication. These studies similarly found that antireflux surgery elevated residual OGJ relaxation pressure (Scheffer *et al.* 2005; Wilshire *et al.* 2012; Hoshino *et al.* 2015; Mello *et al.* 2016) and intrabolus pressure (Scheffer *et al.* 2005; Marjoux *et al.* 2012). These

measures were significantly higher in patients with post-operative dysphagia in 2 studies (Marjoux *et al.* 2012; Wilshire *et al.* 2012), but not significant in another 2 studies (Scheffer *et al.* 2005; Mello *et al.* 2016), while the Hoshino *et al.* study did not assess dysphagia. Limitations of study methods such as post-operative assessment performed too early (at 3 months in Scheffer, Wilshire & Marjoux studies) or at variable timeframe after surgery in the remaining two studies (10 mo to 2.7 yrs), and also inadequate dysphagia assessment and small study numbers erode the authority of these studies.

Timing of assessment and variations of manometric methodology may explain why intrabolus pressure relates to dysphagia in some studies and not others. Variations of surgical technique may also be involved, such as the length and diameter of the OGJ. Several studies have shown that 360° fundoplication results in a longer OGJ compared to healthy controls or reflux disease patients (Pandolfino *et al.* 2005; Kwiatek *et al.* 2010). Also the narrowest width and least distensible part of the OGJ after fundoplication were at the level of the diaphragmatic hiatus (Pandolfino *et al.* 2005; Scheffer *et al.* 2005; Kwiatek *et al.* 2010). Unfortunately the aforementioned studies were conducted in a small number of subjects, ranging from 8 – 12 persons, but are helpful for planning further research. Only one of these studies included patients with dysphagia (Scheffer *et al.* 2005). Intriguingly, from this study, prolonged transit across the OGJ correlated with higher dysphagia scores for solids and liquids (Scheffer *et al.* 2005), but this observation needs to be substantiated. Large well-designed studies are required to establish the interrelationships between opening diameter and length of the OGJ, and measures of OGJ flow resistance (intrabolus and residual relaxation pressure) with regard to dysphagia for solids after antireflux surgery (see section 7.2.2).

The third study (Chapter 4) found a positive correlation between intrabolus pressure, peristaltic amplitude and residual OGJ relaxation pressure, which was independent of fundoplication. This points to an inherent adaptive oesophageal response mechanism to OGJ resistance that is a part of normal OGJ mechanics. This lead to the hypothesis that the oesophagus adapts to increased

OGJ resistance to flow by generating greater oesophageal contractile vigour and that occurrence of dysphagia is related in part to a sub-normal integrated response. This hypothesis is supported by recent HRM studies. Kwiatek *et al.* found that oesophageal contractile vigour (distal contractile integral, DCI) increases in response to outflow resistance i.e. intrabolus pressure (Kwiatek *et al.* 2010). In another study, Marjoux *et al.* found that integrated relaxation pressure (IRP) correlated with intrabolus pressure (Marjoux *et al.* 2012). These two recent HRM studies provide support for an adaptive response to increased OGJ resistance, but further studies are needed to ascertain whether this response is defective in patients with post-operative dysphagia. Studies are needed to examine the hypothesis that oesophageal and OGJ function that fails to modulate to overcome OGJ resistance to outflow elevates the risk of dysphagia after anti-reflux surgery.

The fourth study (Chapter 5) revealed for the first time that some patients have a pre-existing variation of bolus compression and movement in relation to oesophageal peristalsis that increases the risk of troublesome dysphagia after antireflux surgery. Further studies are needed to corroborate these findings (see section 7.2.1).

7.1.4 Aim 4

- **To identify whether the mechanisms of early (<6 weeks) and late dysphagia (≥ 6weeks) are the same or different.**

Several of the presented studies provide insight into the mechanisms of early and late dysphagia after antireflux surgery. The first study (Chapter 2) showed pervading oesophageal ileus immediately after antireflux surgery. It is highly plausible that oesophageal ileus is a major contributing mechanism of early dysphagia. By 3 months post-op, ileus was no longer common.

The third study (Chapter 4) concluded that late dysphagia is at least in part associated with sub-

optimal local intrinsic modulation of oesophageal function in response to altered OGJ mechanics from antireflux surgery. The fourth study (Chapter 5) revealed a subtle but detectable pre-existing anomaly of oesophageal motor function that increases the risk for post-surgical dysphagia. Namely retarded oesophageal flow of a highly compressed viscous bolus ahead of the peak peristaltic contraction.

Recent HRM studies from other laboratories describe varied patterns of oesophageal body motility (frequent failure; weak peristalsis; normal peristalsis) both before and after antireflux surgery, but these studies did not evaluate oesophageal motor patterns in relation to dysphagia status. Nevertheless, residual OGJ pressure correlated significantly with dysphagia (Marjoux *et al.* 2012; Mello *et al.* 2016). It is speculative but the observed change in oesophageal body motility after fundoplication could be the effect of modulation of oesophageal function to new antireflux barrier.

In addition, the first study (Chapter 2) also showed that following 360° fundoplication, mean residual OGJ relaxation pressure with liquid boluses was high at day-1, but was around 36% lower by 3 month testing. The third study (Chapter 4), using the same manometric method in a different group of patients, suggests that 5 months after surgery OGJ residual pressure is about 50% less than at the time of surgery. This gives the impression of progressive 'loosening' of the OGJ/ fundal wrap/ hiatal repair and resistance to flow across the OGJ. This is consistent with a similar finding for OGJ resting pressure measured at the end of surgery and 3 months afterwards (Jamieson & Myers 1992). Allowing time for 'loosening' and adaptation is part of the clinical management strategy for surgical dysphagia before undertaking interventional treatment (Wilshire *et al.* 2012).

Taken together, the above findings of the first and third study (Chapters 2 & 4) suggest that the same mechanisms probably contribute to both early and late dysphagia, with the exception of oesophageal ileus, but with varying importance relative to time after surgery. It is proposed that

for early dysphagia during the peri-operative period, oesophageal ileus is likely to be very important and then reduce over an unknown timeframe. The data on residual OGJ relaxation pressure over time strongly suggests that tissue oedema is likely to play a big role in dysphagia early on after surgery. For late dysphagia, abnormally high residual OGJ pressure at or beyond 6 months after surgery is unlikely to be due to oedema and more likely to represent the permanent effects of fundoplication and hiatal repair in bolstering OGJ pressure. If sub-optimal modulation of oesophageal response to surgically altered OGJ mechanics occurs, then it is likely that transit across the OGJ is altered or impaired and this will intermittently or always give rise to dysphagia.

7.1.5 Aim 5

- **To explore the relationship between pressures of oesophageal peristalsis and the movement of a swallowed bolus traversing the oesophagus with regard to dysphagia before and after antireflux surgery.**

The fourth study (Chapter 5) presents novel analysis that quantifies how far ahead of the peak peristaltic wave a bolus is and the degree to which the bolus is compressed. This activity is summarised by the Dysphagia Risk Index (DRI). Thus for the first time, on a second-by-second basis, the effects of peristalsis on bolus propulsion and luminal resistance to bolus passage are integrated. This automated analysis of impedance-manometry for viscous swallows revealed subtle differences in the pressure-flow relationship, a 'pressure-flow mismatch', not detected by previous analytical methods. Critically, this new analysis identified patients before surgery that were at risk of dysphagia after surgery.

Subsequent application of this analysis to a paediatric population has demonstrated pressure-flow mismatch and an elevated DRI in children before antireflux surgery that also predicts dysphagia afterwards (Loots *et al.* 2013). This confirms the findings of the fourth study in adults

and supports this methodological approach for analysis of simultaneous impedance-manometry recordings (Chapter 5). In a further study, patients with dysphagia of no known cause had higher DRI compared to healthy controls. In addition, the DRI was found to be higher for individual swallows during which subjects perceived there was resistance to bolus passage (Chen *et al.* 2013).

The most significant findings of the fourth study were for viscous swallows. This indicates that the compact movement of a viscous bolus is a better stimulus for revealing the subtle aberrations of pressure-flow interactions with regard to dysphagia. This finding also resonates with the recurring observation that dysphagia to solids is the most common problem after antireflux surgery. It remains exceptional for oesophageal motor function to be tested with solid boluses. For instance, recently published normal HRM-derived values after fundoplication were only for series of 10 water swallows of 5mL or 10 mL each (Hoshino *et al.* 2015; Weijenborg *et al.* 2015).

HRM protocols with a solid test bolus although rare, are slowly emerging, so perhaps we're on the cusp of change. In a recent study by Wang *et al.*, patients with persistent dysphagia after antireflux surgery had HRM performed while sitting. Abnormalities of oesophageal function were revealed with a solid test meal (cheese & onion pasty) more often than with liquid or multiple rapid swallows. These abnormalities included outlet obstruction (41%) and hypodynamic or fragmented motility (30%). Three study limitations prevent better interrogation of the data. First, dysphagia was inadequately assessed, as there was no record of dysphagia severity. Second, there was no documentation of the type of antireflux surgery performed. Third, neither imaging nor impedance were used, so impaired OGJ outflow could only be inferred from manometric assessment. Limitations aside, this study demonstrates that a solid test meal was a greater challenge to oesophageal function for bolus passage through the OGJ/fundal canal, than liquid swallows. In contrast to findings of the third study (Chapter 4), Wang *et al.* did not find a higher mean IRP (HRM equivalent of residual OGJ pressure) for water

swallows in the dysphagia group compared to asymptomatic patients. Although for solids, 41% of dysphagia patients had an abnormally high IRP (>25 mmHg), compared to 0% for healthy controls (Wang *et al.* 2015). Future HRM and high-resolution impedance-manometry (HRIM) studies with a standardised viscous or solid test stimulus in patients with troublesome surgery-related dysphagia are highly desired and eagerly awaited.

There are recently described alternative approaches to manometric evaluation of oesophageal function with the aim of identifying patients susceptible to post-operative dysphagia. One such approach is the use of multiple rapid swallows to induce peristaltic inhibition and then a subsequent vigorous, rebound peristaltic contraction (Fornari *et al.* 2009; Daum *et al.* 2011). After 360° fundoplication, patients with post-operative dysphagia were shown to have an abnormal multiple rapid swallow response, with less contractile vigour of the oesophageal smooth muscle segment (Stoikes *et al.* 2012; Shaker *et al.* 2013). The ideal protocol and validity of this testing is the focus of current research (Price *et al.* 2014).

There are no other comparative studies of integrated impedance-manometry analysis in patients with dysphagia after antireflux surgery. An alternative approach to combined analysis, also based on intrabolus pressure, is being developed to assess intrabolus pressure and flow in 4 regions of the oesophagus (Lin *et al.* 2014b). In a separate study, OGJ bolus flow in reference to OGJ nadir impedance and the flow permissive time excluding inspiratory crural contractions was recently described (Lin *et al.* 2014a). These promising studies with concurrent HRIM-fluoroscopy for validation of HRIM based pressure-flow interactions were unfortunately limited to observations in 10 - 25 healthy controls. Studies in clinical groups are anticipated. Of most interest are before and after studies in patients undergoing revisional surgery for troublesome dysphagia related to previous antireflux surgery.

7.1.6   Aim 6

- **To explore, in greater detail than has occurred previously, the mechanics of the OGJ by measurement of radial pressure patterns along the length of the OGJ with regard to dysphagia after antireflux surgery.**

The factors that uncover sub-optimal function and modulation of the oesophagus in patients with post-operative dysphagia undoubtedly relate to changes within the OGJ at surgery. The fifth study (Chapter 6) presents 3-D pressure maps of the OGJ, which reveal for the first time localised significantly greater inspiratory OGJ pressure in patients with troublesome dysphagia after 90° and 360° fundoplication. This is consistent with a focally restrictive diaphragmatic hiatus.

At this time there are no comparative studies to discuss. Future studies are outlined in section 7.2.3.

7.2 FUTURE DIRECTIONS

Some key directions for further research can be identified from the studies presented:

7.2.1 Predicting post-operative dysphagia

The potential of automated impedance manometry (AIM) analysis with viscous swallows to characterise pressure-flow dynamics needs to be realised. If the findings of the fourth study (Chapter 5) are replicated by a prospective high-resolution impedance-manometric (HRIM) study, then AIM analysis will be established as the only pre-operative test that can identify patients at risk of developing dysphagia after antireflux surgery. Further validation is warranted. Additional studies are necessary to assess viscous bolus movement during concurrent HRIM with fluoroscopy to determine the validity of AIM analysis variables, especially with regard to dysphagia.

7.2.2 Influence of OGJ dimensions on post-operative dysphagia

The studies presented raise the question of whether the length and opening diameter of the OGJ after antireflux surgery influence intrabolus pressure and residual OGJ relaxation pressure, particularly in patients with surgery-related dysphagia. Understanding factors affecting flow and resistance to flow through both the oesophageal body and the OGJ may bring about formulation of a multi-factorial algorithm that better discriminates patients with and without post-operative dysphagia. A future study using EndoFLIP® or fluoroscopy and HRIM with multiple standardised viscous or semi-solid boluses to measure OGJ compliance, opening, and flow characteristics in patients with and without dysphagia, before and after surgery, will go someway towards resolving this unanswered question. The EndoFLIP method is especially promising, as it does not involve use of ionizing radiation, yields numerical data without laborious image analysis and does not require the inputs of a now rare radiologist expert in

contrast radiology of the oesophagus.

7.2.3   Calibration of hiatal repair to reduce surgery-related dysphagia

Methods for calibration of hiatal repair need to be developed, compared and critically appraised. The most promising methods then need to be assessed for their efficacy in reducing surgery-related dysphagia.   In addition, HRM assessment of OGJ function in response to inspiratory effort is needed to determine the functional implications of hiatal repair in patients with and without surgery related dysphagia.   Such measurements have the potential for recognizing a 'snug' hiatus prior to revisional surgery in patients with troublesome dysphagia.

A chronically unresolved issue in this field of research is the wide use of technically inadequate assessment of dysphagia. Published reports are often imprecise with respect to the definition of dysphagia, the grading of symptoms, and the timing of study. Studies frequently use different assessment methods for dysphagia, which severely limits comparison among studies. Guidelines are needed for standardised assessment of early and late dysphagia to improve the quality of clinical assessments, to facilitate further research and to enable more confident comparisons of data from different studies.

In the ideal world, antireflux surgery with hiatal repair and fundoplication will reduce gastro-oesophageal reflux without perception of impaired passage of swallowed substances into the stomach.   The use of new measures of swallowing function and OGJ mechanics along with attention to hiatal repair hold promise for reducing post-operative dysphagia and bringing the ideal operation a step closer.

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APPENDICES

On the pages following are the appendices listed below:

Appendix A: Awards and Prizes

Appendix B: List of published abstracts and scientific communication

Appendix C: List of other publications during candidature

APPENDICES

APPENDICES

Appendix A: Awards and Prizes

The following awards were received for oral presentations of study findings presented in this thesis:

2007   **Oral Presenter Award** and **Poster Prize,** Winner & Dean's Certificate of Merit, inaugural Faculty of Health Science Research Expo. 23rd October, 2007, Bonython Hall, Adelaide

2008   **Science Excellence Awards SA**, Finalist, for Research Initiatives Informing Clinical Practice, SA Health. 4th June, 2008, Adelaide.

2011   **Best Oral Presentation Prize**, Winner, for original research presented at International Society for Diseases of the Esophagus Australasian Section (IsDEAS). 18th February 2011, Hobart.

2011   **3-Minute Thesis Competition Prize**, 2nd Place, Faculty of Health, Best Oral presentation at the Postgraduate Research Conference, National Wine Centre, 25th August, 2011, Adelaide.

2012   **Ross Wishart Award**, for the most outstanding presentation by a young investigator at ASMR Medical Research Week® Adelaide Convention Centre, 6th June, 2012, Adelaide.

2014   **SA Medical Scientists Graduate Research Award**, competitive award following peer review for forefront medical science research. 16th July, 2014.

APPENDICES

Appendix A (continued)

3-Minute Thesis Competition: This competition challenges higher degree research students to present a compelling oration on their thesis topic and its significance within 3-minutes, using one slide and in language appropriate to an intelligent but non-specialist audience.

2011   **3-Minute Thesis Competition Prize**, 2nd Place, Best Oral presentation.
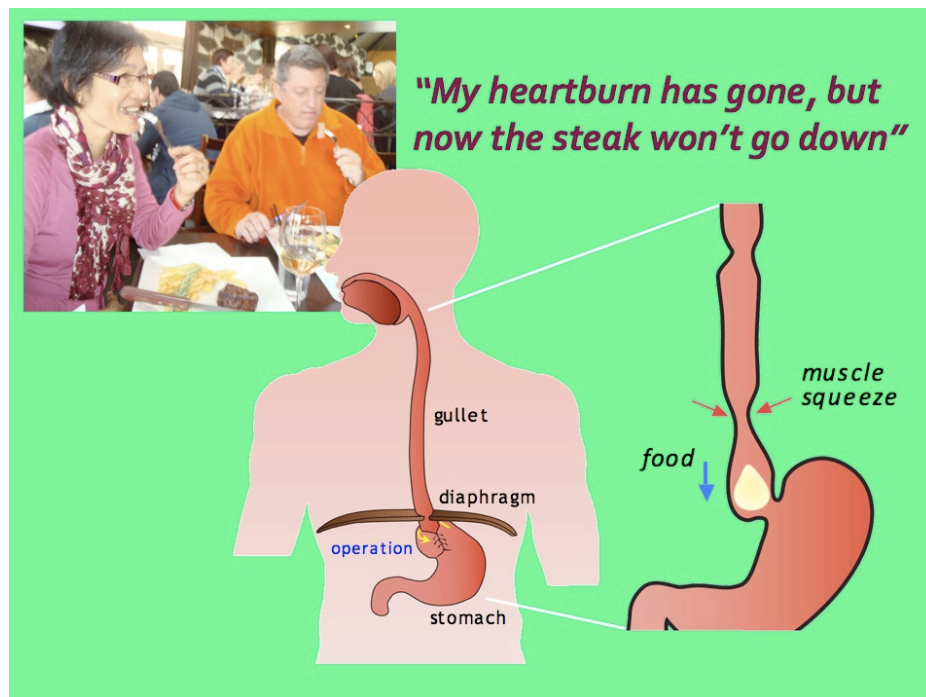
APPENDICES

Appendix A (continued)

Media article: Following the Dean's award, an Invitation was received to submit an article *(The University of Adelaide & Royal Adelaide Hospital media liaison officers approved the text prior to submission).*

2008   '**Fire down below'** was published in: *"Can you believe it?"* column of the Saturday Review section of '*The Advertiser'*, Adelaide daily newspaper, Saturday 3rd May, 2008.

        Erratum: 'with Jenny Myers'

Fire down below

When surgery is the only answer to heartburn.

TOO much wining and dining has many of us reaching for the antacid. These symptoms show us how our body responds to rich food and drink. Belching after eating often results in venting of gas and reflux of acid from the stomach into the gullet (oesophagus). It is the acid which irritates the cells in the gullet and is associated with heartburn. For most, this scenario occurs infrequently. But imagine if many meals were causing discomfort.

The key to understanding burping and heartburn is a muscular valve which is the gateway to the stomach. This is a two-way valve: it opens to let swallowed substances into our stomach and it also opens when we burp to let gas out of the stomach. At other times, the muscular valve is closed to protect the gullet from the stomach contents.

When many meals cause discomfort regardless of what we eat, the muscular valve is probably behaving abnormally.

When frequent or severe symptoms occur, tests are performed to assess the strength and function of this valve. Using highly specialised equipment (manometry), the squeeze pressures of the swallowing muscles as well as the muscular valve pressure are assessed. In addition, acid reflux testing (pH test) evaluates the occurrence of acid reflux and the incidence of symptoms. These tests are used clinically to help doctors with the diagnosis and management of reflux disease and swallowing disorders.

These tests frequently show us that the muscular valve that opens at the top of your stomach to let swallowed substances into the stomach has ongoing loss of strength or relaxes inappropriately, allowing stomach acid to wash backwards. We have drugs to reduce the amount of acid produced in the stomach, which means less acid is likely to be refluxed with a burp and heartburn is reduced. The term "heartburn" is unfortunate and confusing, for it is not "burning in the heart" but "burning in the gullet".

So far, the only way we have of strengthening the valve is by an operation. Laparoscopic or key-hole anti-reflux surgery is commonly performed and involves the wrapping of a small portion of the stomach around the muscular valve to give it strength and support. This operation prevents reflux and it also prevents burping. But sometimes we want to burp. Ideally, the operation needs to give optimal balance by

Reap what you eat
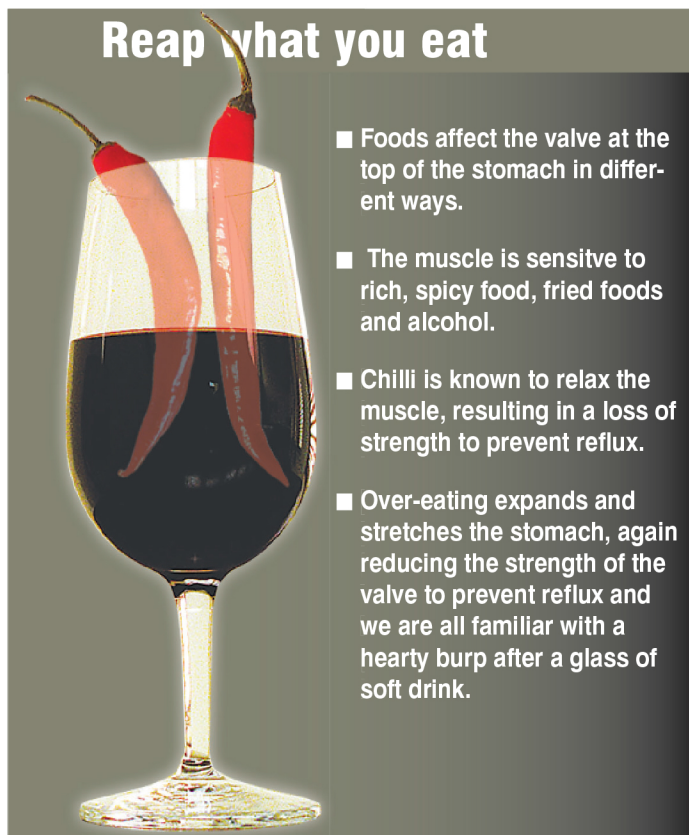
- Foods affect the valve at the top of the stomach in different ways.

- The muscle is sensitve to rich, spicy food, fried foods and alcohol.

- Chilli is known to relax the muscle, resulting in a loss of strength to prevent reflux.

- Over-eating expands and stretches the stomach, again reducing the strength of the valve to prevent reflux and we are all familiar with a hearty burp after a glass of soft drink.

reducing reflux without inhibiting burping. The focus of a team of researchers from the University of Adelaide is to evaluate the criteria needed for this operation to achieve the best results. Studies so far show us that when the stomach is wrapped all the way around the muscular valve, reflux is stopped but the ability to burp is often lost.

When the stomach is wrapped partly around the muscular valve, most reflux is stopped and the ability to burp is retained.

One size does not fit all when it comes to anti-reflux surgery. The choice of operation often comes down to a simple question: To burp or not to burp? Ongoing investigations into the techniques used during the operation, measurements of the muscular valve function after surgery and the long-term effectiveness of the surgery to prevent reflux will lead to better surgery, better reflux (valve) control and better enjoyment of wine and food.

Jenny Myers is clinical scientist in the Surgical and Specialties Service at Royal Adelaide Hospital and a PhD candidate in the Discipline of Surgery at the School of Medicine, University of Adelaide.

APPENDICES

Appendix B: Published abstracts and scientific communication

The abstracts below were accepted for oral presentation (O) or poster (P) unless otherwise indicated and presented at a local, national or international scientific meeting by the <u>presenting author</u>:

1. **Myers JC**, Jamieson GG. (P)
    Technique: The radial pressure profile of the lower oesophageal sphincter after partial and total fundoplication. Proceedings of 10th World Congress of the International Society of Diseases of the Esophagus. Adelaide 22-25th February, <u>2006.</u>

2. **Myers JC**, Jamieson GG. (P)
    Insights into post-operative dysphagia following total and partial laparoscopic fundoplication. J Gastroenterol & Hepatol <u>2006</u>; 21 (suppl 4): A340.

3. **Myers JC**, Jamieson GG. (O)
    Determining the manometric and anatomic features which influence distal oesophageal ramp pressure. Aust NZ J Surg <u>2007</u>; 77 (suppl 1): A43.

4. <u>Lamb PJ</u>, **Myers JC**, Jamieson GG, Thompson SK, Devitt PG, Watson DI. (O)
    Long-term outcomes of revisional surgery following laparoscopic fundoplication for gastro-oesophageal reflux disease. Proceedings of 11th World Congress of the International Society of Diseases of the Esophagus. Budapest 10-13th September, <u>2008</u> ISBN 978-88-7587-465-0.

5. **Myers JC**, Jamieson GG. (O)
    Manometric distal oesophageal ramp pressure and dysphagia in healthy controls, reflux and post fundoplication subjects. Proceedings of the 11th World Congress of International Society of Diseases of the Esophagus. Budapest 10-13th September, <u>2008</u> ISBN 978-88-7587-465-0.

6. **Myers JC**, Jamieson GG, Thompson SK, Devitt PG. (O)
    Manometric evaluation of post fundoplication dysphagia utilising water swallows and bread swallows. Proceedings of the IsDEAS, Maroochydore QLD 19-21 February, <u>2009</u>.

7. **Myers JC**, Jamieson GG, Thompson SK, Devitt PG. (O)
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8. **Myers J**, Van't Hek J, Omari T, Dent J, Nguyen NQ, Jamieson GG. (O)
    More sophisticated analysis of oesophageal function may be leading to clinically useful results. ANZ J Surg <u>2011</u>; 81 (suppl 1): A92.

9. **Myers JC**, Van't Hek JE, Jamieson GG, Dent J, Nguyen NQ, Ching K, Holloway RH, Omari TI. (P)
    Automated impedance manometry showing variation in esophageal function pre-operatively is associated with dysphagia after fundoplication. Gastroenterology <u>2011</u>; 140 (5): S-298.

10. **Myers JC**, Van't Hek JE, Jamieson GG, Dent J, Nguyen NQ, Ching K, Holloway RH, Omari TI. (O)
    Dysphagia risk index: predicting dysphagia after fundoplication using a computational algorithm of impedance/manometry. Proceedings of the Surgical Research Society of Australasia, 48th Annual Meeting 11th November, <u>2011</u>; p17. Published online at ANZ J Surgery website: www.anzjsurg.com/view/0/SRS.html

11. **Myers JC**, Dent J, Jamieson GG, Omari TI. (O)
    Predicting swallowing difficulty after anti-reflux surgery. Proceedings for the Annual Scientific Meeting of the ASMR SA Division. <u>2012</u>; RW3: pp 33-34.

12. **Myers JC**, Jamieson GG, Dent J, Omari TI. (O)
    Risk of dysphagia after fundoplication recognised with high-resolution impedance/ manometry. Dis Esoph <u>2012</u>; 25 (suppl 1): 47A.

13. **Myers JC**, Dent J, Jamieson GG, Omari TI. (O)
    Troublesome dysphagia after fundoplication linked to novel measures of pre-existing oesophageal function. Proceedings of the IsDEAS, Melbourne VIC 7-9 February, 2013.

14. Omari TI, Kritas S, **Myers JC**. (O)
    The mechanics of esophageal bolus transport are altered in subjects reporting perception of solid bolus hold up. Gastroenterology 2013; 144 (5 suppl 1): S-95.

15. **Myers JC**, Jamieson GG, Dent J, Omari TI. (O)
    Dysphagia after fundoplication and pre-existing esophageal function. Proceedings of International Surgical Week ISW Sept 2013; Online published abstract: http://flippingbook.nuboprepress.com/isw2013/web/

16. **Myers JC**, Omari TI. (P)
    Esophageal impedance measured during peak peristaltic contraction correlates with endoscopic findings of mucosal inflammation in patients with gastro-esophageal reflux symptoms. Gastroenterology 2014; 146 (5 suppl 1): S-752.

17. Nguyen NQ, Singendonk MJ, **Myers JC**, Tippett M, Bambrick J, Holloway RH, Omari TI. (P)
    Automated high-resolution impedance manometry analysis detects subtle esophageal motor dysfunction in patients who have non-obstructive dysphagia with normal manometry/ impedance study. Gastroenterology 2014; 146 (5 suppl 1): S-685.

18. **Myers JC**, Estremera FA, Jamieson GG, Dent J. (O)
    The effect of fundoplication on radial pressure of the anti-reflux barrier and dysphagia. Proceedings of ANGMA, Monash University, Melbourne. 28 Mar, 2014.

19. **Myers JC**, Estremera-Arévalo F, Jamieson GG, Dent J. (O)
    Impact of fundoplication type on radial pressure of the anti-reflux barrier and dysphagia. Dis Esoph 2014; 27 (suppl 1): 12A.

20. **Myers JC** and Dent J. (Letter to the Editor)
    A case of post fundoplication dysphagia: Another possible interpretation of the manometric findings. *J Neurogastroenterol Motility* 2014; 20(4): 561.

Scientific collaboration arising from a study presented:

2012-14   **AIMIGOS, Automated Impedance Manometry Investigator Group On Swallowing**. An international collaboration for evaluation and development of AIM. This collaboration of eleven investigators spanned several continents, including Europe (Belgium; England), North America (Illinois, Houston, Ohama in the USA) and Australia (Adelaide).

APPENDICES

Appendix C: Other publications during candidature

I was a co-investigator and co-author for the following studies and publications during candidature:

1. Wayman J, **Myers JC**, Jamieson GG.
    Preoperative gastric emptying and patterns of reflux as predictors of laparoscopic fundoplication outcome. *Br J Surg* 2007; 94(5): 592-8.

2. Thompson SK, Jamieson GG, **Myers JC**, Chin KF, Watson DI, Devitt PG.
    Recurrent heartburn after laparoscopic fundoplication is not always recurrent reflux. *J Gastrointest Surg* 2007; 11(5): 642-7.

3. Yang H, Watson DI, Kelly JJ, Lally CJ, **Myers JC**, Jamieson GG.
    Esophageal manometry and clinical outcome after laparoscopic Nissen fundoplication. *J Gastrointest Surg* 2007; 11: 1126-33.

4. Grotenhuis BA, Wijnhoven BPL, **Myers JC**, Jamieson GG, Devitt PG, Watson DI.
    Re-operation for dysphagia after cardiomyotomy for achalasia. *Am J Surg* 2007; 194: 678-82.

5. Wijnhoven BPL, Lally CJ, Kelly JJ, **Myers JC**, Watson DI.
    Use of anti-reflux medication after antireflux surgery. *J Gastrointest Surg* 2008; 12: 510-17.

6. Wong ASY, **Myers JC**, Jamieson GG.
    Esophageal pH profile following laparoscopic total fundoplication compared to anterior fundoplication. *J Gastrointest Surg* 2008; 12: 1341-5.

7. Chin KF, **Myers JC**, Jamieson GG, Devitt PG.
    Symptoms experienced during 24 hour pH monitoring and their relationship to outcome after laparoscopic total fundoplication. *Dis Esoph* 2008; 21: 445-51.

8. Thompson SK, Cai W, Jamieson GG, Zhang AY, **Myers JC**, Parr ZE, Watson DI, Persson J, Holtmann G, Devitt PG.
    Recurrent symptoms after fundoplication with a negative pH study – Recurrent reflux or functional heartburn? *J Gastrointest Surg* 2009; 13: 54-60.

9. Lamb PJ, **Myers JC**, Thompson SK, Jamieson GG.
    Laparoscopic fundoplication in patients with a hypertensive lower esophageal sphincter. *J Gastrointest Surg* 2009; 13: 61-65.

10. Wong IWY, Rees G, Greiff L, **Myers JC**, Jamieson GG, Wormwald PJ.
    Gastroesophageal reflux disease and chronic sinusitis: in search of an esophageal-nasal reflex. *Am J Rhinol Allergy* 2010; 24: 255-9.

11. Broeders JA, Sportel IG, Jamieson GG, Nijjar RS, Granchi N, **Myers JC**, Thompson SK.
    Impact of ineffective oesophageal motility and wrap type on dysphagia after laparoscopic fundoplication. *Br J Surg* 2011; 98: 1414-21.

12. Raeside MC, Madigan D, **Myers JC**, Devitt PG, Jamieson GG, Thompson SK.
    Post-Fundoplication Contrast Studies: Is There Room for Improvement? *British Journal of Radiology* 2012; 85: 792-9.

13. Griffiths E, Devitt PG, Jamieson GG, **Myers JC**, Thompson SK.
    Laparoscopic stapled cardioplasty for end-stage achalasia. *J GI Surg* 2013; 17: 997-1001.

14. Omari TI, Wauters L, Rommel N, Kritas S, **Myers JC**.
    Esophageal pressure-flow metrics in relation to bolus volume, bolus consistency and bolus perception. *UEG Journal* 2013; 1(4): 249-258.

15. Rohof WO, **Myers JC**, Estremera FA, Ferris LS, Van de Pol J, Boeckxstaens GE, Omari TI.
    Inter and intra-rater reproducibility of esophageal automated impedance manometry analysis.
    Neurogastroenterol Motil <u>2014</u>: 26(2): 168-75.

16. Gossage JA, Devitt PG, Watson DI, **Myers JC**, Jamieson GG, Thompson SK.
    Surveillance endoscopy at five years or more after cardiomyotomy for achalasia*. Ann Surg* <u>2014</u>:
    259(3): 464-8.

17. Omari TI, Szczesniak MM, Maclean J, **Myers JC**, Rommel N, Cock C, Cook IJ.
    Correlation of esophageal pressure-flow analysis findings with bolus transit patterns on
    videofluoroscopy. *Dis Esophagus*, Epub 17 Dec, <u>2014</u>, DOI: 10.1111/dote.12300.

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