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Susceptibility to dysphagia after fundoplication revealed by novel automated impedance manometry analysis

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Automated analysis findings were presented at Digestive Diseases Week, May 2011 and published in abstract form in Gastroenterology 2011; 140 (5 suppl 1): S-298.

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; IRP, integrated relaxation pressure; BPT, bolus presence time; TBTT, total bolus transit time; msu, median standardized units; DRI, dysphagia risk index; IQR, inter-quartile range.

SHORT RUNNING HEADER: Susceptibility to fundoplication dysphagia

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ABSTRACT

**Background:** To evaluate dysphagia in relation to bolus movement in patients undergoing 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 & bolus movement variables. An iterative analysis determined if any variables were altered in relation to dysphagia. Standard measures of esophago-gastric junction (EGJ) pressure, bolus presence time (BPT) and total bolus transit time (TBTT) were also evaluated. **Key Results:** At 5 months post-op, 15 patients had some dysphagia, including 7 with new-onset dysphagia. For viscous boluses, three AIM-derived pressure-flow variables recorded pre-operatively varied significantly in relation to post-operative 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) of esophageal dysfunction (DRI = IBP*IBP_slope/TNadImp-PeakP). DRI values derived from pre-operative measurements were significantly elevated in those with post-operative 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 post-operative dysphagia. Thus susceptibility to post-fundoplication dysphagia is related to a pre-existing sub-clinical variation of esophageal function.

(Word count = 249 words)

**KEY WORDS:** anti-reflux surgery, dysphagia, esophago-gastric junction, esophagus, impedance, laparoscopic fundoplication.
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 is unclear [1]. A modest reduction in the prevalence of dysphagia after fundoplication has been achieved through modifications to operative technique. Meta-analyses of outcomes suggest a partial fundoplication results in less dysphagia and less revisional surgery than a total fundoplication [2-4]. Currently however, pre-operative testing is 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, particularly of viscous boluses, would be expected in patients with dysphagia. Intraluminal electrical impedance recordings, which detect bolus flow, have been used to define overall bolus transit time and bolus presence time at several levels in the esophagus [9]. Counter-intuitively, synchronous contractions and failed peristalsis are frequently associated with complete bolus transit [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 post-operative dysphagia [6]. Thus neither intraluminal pressures alone nor measures of bolus presence are adequate to predict dysphagia.

Thus far, no analysis of post-fundoplication 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 post-fundoplication 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 pre-operative 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 cerebro-vascular 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 24hr 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 anti-reflux 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 9 food types with increasing viscosity (water to meat; scale 0- 45) [14]. All patients underwent a barium swallow on day one and 5 months after surgery (same day as impedance/manometry) to identify anatomical abnormalities (recurrent hiatal hernia; wrap migration). Patients with post-operative 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 8 channel water-perfused catheter (0.3mL min^{-1}) with 4 paired impedance rings, built specifically (by TIO) for this study. Manometric side holes at 5cm, 10cm, 15cm and 20cm above the EGJ were matched with pairs
of 4 mm long electrical impedance rings built into the catheter, 2 cm apart at 4 & 6 cm, 9 & 11 cm, 14 & 16 cm and 19 & 21 cm above the EGJ. 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 (<6 $\mu$A) alternating current.

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 trans-nasally to the stomach following topical nasal anaesthesia (5% lignocaine HCl). With patients in the right lateral position, the sleeve was positioned across the EGJ and fixed at this level by taping it to the nose. A 10-min rest period was followed by: ten, 5 mL liquid swallows (normal saline) and ten, 5 mL viscous swallows (low impedance EFT-viscous swallow challenge medium, Sandhill Scientific, Highland Ranch, CO, USA) given at 30 s intervals.

**Data analysis**

Data were evaluated by conventional analysis and by the new AIM analysis.

*Conventional analysis of manometry and impedance data*

Using Bioview software (v 5.3.4 Sandhill Scientific, Highland Ranch, CO, USA), 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 (mmHg, maximum or plateau pressure prior to peristaltic upstroke), both referenced to end-expiratory esophageal baseline, were determined for each bolus swallow [16].

For evaluation of esophageal bolus transport in the span of paired esophageal impedance rings, the bolus presence time (BPT, s) was determined as the interval between the bolus entry time (50% drop from 3-sec pre-swallow 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 TBBT 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 boluses 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].

**Automated Impedance manometry analysis**

Raw manometric and impedance data for each test bolus over a 30 s window were exported in ASCII text format, then analysed using MATLAB (version 7.9.0.529 R2009b, MathWorks 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 (Figure 1A). The raw impedance data were standardised to the median impedance and reported as median standardised 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 analysed in separate pressure-impedance plots (Figure 1B). Esophageal pressures during swallowing were referenced to pre-swallow esophageal baseline pressures. The time interval between nadir esophageal impedance (TNadImp, s) and peak esophageal pressure (TPeakP, s) was automatically determined at all positions along the impedance-pressure array (Figure 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. Guided by TNadImp and TPeakP, the following variables were also determined and averaged for both the entire and distal half of impedance-pressure array:

i) pressure at TNadImp (PNadImp, mmHg) (Figure 1C); ii) pressure at TPeakP (PeakP, mmHg) (Figure 1C); iii) intra-bolus pressure (IBP, mmHg), estimated by calculating the median pressure recorded...
from NadImp to the midpoint in time of TNadImp-PeakP (Figure 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 esophago-gastric junction pressures**

The cumulative duration of EGJ relaxation was plotted from the minimum to the maximum pressure and used to calculate the 4 s integrated relaxation pressure (4 s IRP) [17]. Resting EGJ pressure (mmHg) was recorded for 10 seconds 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 pre-operative viscous swallows that were significantly associated with post-fundoplication 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 a wider numeric scale. The combined variables form the esophageal dysphagia risk index (DRI) by the formula: intra-bolus pressure multiplied by slope of intra-bolus pressure rise in the distal esophagus, divided by the time interval between the nadir impedance and peak pressure in the distal esophagus.

\[
DRI = \frac{\text{IBP} \times \text{Distal_IBP slope}}{\text{Distal_TNadImp-PeakP}}
\]

The DRI was calculated for pre & post-operative viscous and liquid bolus swallow data. Further, DRI was evaluated for patients according to their pattern of dysphagia: patients with (1) no dysphagia either pre or 5mo post-operatively; (2) dysphagia before and after fundoplication; and (3) dysphagia post-op 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) in whom AIM analysis and DRI calculation was undertaken. 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 gastro-intestinal symptoms.

**Laparoscopic fundoplication**

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

**Statistical analysis**

Normally distributed data are presented as mean ± SE and for non-parametric data, the median with inter-quartile 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 ≤ 0.10 for descriptive data to identify parameters of interest and p < 0.05 for pressure-flow variables described above. Analysis of variance testing, ANOVA or Kruskal-Wallis, with multiple comparison post-hoc Dunn’s or Holm-Sidak method were applied for comparison of patients grouped by dysphagia status. For this analysis, a patient was positive for dysphagia when their dysphagia composite score was greater than zero. Sensitivity and specificity were determined for pressure-flow variables and dysphagia risk index. Cohen’s kappa-statistic is reported, where kappa value of 0.00 is no agreement, 0.00-0.20 slight, 0.21-0.40 fair, 0.41-0.60 moderate, 0.61-0.80 substantial, 0.81-1.00 near perfect agreement.
RESULTS

Total fundoplication was performed in 8 patients and 11 chose a partial fundoplication. Surgery was efficacious with 95% of patients experiencing less heartburn (no heartburn 13/19, reduced heartburn 5/19, similar heartburn 1/19 patients) and 84% experiencing less regurgitation (16/19 patients). Three patients recorded identical pre & post-operative scores for low-medium grade regurgitation (1/10, 2/10, 5/10), but all three reported a reduction in heartburn post-operatively.

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 75% of patients experiencing dysphagia ‘sometimes’ for eggs, fish, bread, apple & steak. Five months after surgery, 15 patients reported dysphagia (79%), including seven with new-onset dysphagia ‘sometimes’ for solids (Figure 2). Overall, more patients reported dysphagia after fundoplication, but the median composite dysphagia score was not significantly higher (0, IQR 0 – 13.5 pre-op vs 4, IQR 1-15 post-op, p = 0.28). Seven of 15 patients reported a post-operative dysphagia score < 5 out of a possible 45 (this equates to experiencing occasional dysphagia for one food type, either bread, apple or steak). For patients with dysphagia both before and after surgery, 50% of patients experienced the same or worse dysphagia post-operatively for bread, apple & 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 pre & post-op) and another at 17 months (good relief of symptoms; note: low DRI pre & post-op). No abnormality was identified at endoscopy. No patient underwent surgical revision for dysphagia.

Barium swallows on Day 1 and 5 months after surgery showed the fundoplication was intact and was 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. Repeat barium swallow another 24 h later, and 5 months subsequently were unremarkable.
The effects of fundoplication on esophageal function

Baseline measurements showed that 4 of 19 (21%) patients had abnormal esophageal transit pre-operatively (see methods). Liquids traversed the esophagus more quickly than viscous boluses (pre op 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 (Table 1, 2).

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 pre-operatively, showed normal transit post-operatively. 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 supplementary data in Appendix A online). In particular, 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 supplementary data in Appendix A online).

Pre-operative impedance/manometry data and dysphagia after surgery

Data were explored to determine if 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 post-operative dysphagia for both liquid and viscous swallows.

AIM analysis of pre-operative data revealed three pressure-flow variables for viscous boluses that varied significantly with regard to dysphagia (Table 3). Patients with post-operative dysphagia had significantly greater IBP, IBP_slope and significantly shorter TNadImp-PeakP pre-operatively compared to those without dysphagia after surgery. With liquid boluses, only pre-operative TNadImp-PeakP was significantly shorter in patients with post-operative dysphagia.
Dysphagia Risk Index

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

An evaluation of pre-operative viscous swallow data and dysphagia found DRI was highest in patients with ‘new onset’ dysphagia after surgery (Table 4, Figure 3). While the DRI for patients with dysphagia both before and after surgery was significantly higher than control subjects, it was not significantly greater for patients with no dysphagia, despite the same group mean DRI (Table 4). However, the three esophageal variables showed high sensitivity and specificity (Figure 4). Based on these data, optimal predictive value for DRI is >14 which has a sensitivity of 75%, a specificity of 93% and kappa statistic of 0.68 i.e. substantial agreement (Figure 4). 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 post-operative dysphagia (sensitivity 50%, specificity 14%, kappa statistic 0.00).

Pre-operative impedance/manometry data and dysphagia prior to surgery

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

AIM analysis of patients with dysphagia prior to surgery showed that only pre-operative PeakP for viscous boluses was significantly lower in patients with dysphagia (31mmHg, IQR 4-45 vs 51mmHg, IQR 39-68, p = 0.02). For viscous boluses before surgery variation in DRI for the presence/
absence of dysphagia before surgery did not reach statistical significance. Some trends were observed for responses to liquid boluses: patients with dysphagia tended to show greater IBP in the distal esophagus (8mmHg, IQR 4-13 vs 5mmHg, IQR 3-7, p = 0.05) and shorter TNadImp-PeakP (3.1 ±0.4 s 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 dysphagia prior to surgery did not reach statistical significance (12, IQR 1-69 with dysphagia vs 2, IQR 0-15 no dysphagia).

Post-operative impedance/manometry data and dysphagia after surgery

Though post-operative testing showed that BPT and TBTT were significantly longer (Table 1), these measures did not correlate with dysphagia after surgery. Interestingly, after surgery 9 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 intra-luminal pressures, although altered by fundoplication (Table 2, see supplementary data in Appendix A online), did not vary according to the presence of dysphagia after surgery.

AIM analysis of post-operative data showed that viscous bolus esophageal PeakP was significantly lower in patients who developed post-op dysphagia (44 ±4 mmHg vs 68 ±5 mmHg, p = 0.01). Similarly, liquid bolus esophageal PeakP showed a trend for being lower in patients with dysphagia (48 ±5 mmHg 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 8 patients, but neither DRI, AIM or conventional variables were significantly different in relation to a small hernia.

DRI for post-operative liquid and viscous swallows did not vary significantly in relation to the type of fundoplication i.e. partial and total fundoplication. This is in accordance with the finding that post-operatively esophageal pressure-flow variables did not vary significantly for fundoplication type. Fundoplication significantly raised both EGJ residual pressure during swallowing and distal intra-
bolus pressure, consistent with increased impediment to flow across the junction (total > partial fundoplication, see supplementary data in Appendix B online). Though surgery generally prolonged BPT at all esophageal segments and TBTT for liquid and viscous boluses for both types of fundal wrap (see supplementary data in Appendix C online), there was no significant difference between the wrap types and these changes did not correlate with the presence of 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 findings recognise pre-operative derivation of the Dysphagia Risk Index (DRI) for viscous boluses will help identify patients at risk of post-fundoplication dysphagia and warrants further study.

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 post-fundoplication dysphagia is mostly for solids. However it is important to recognise that in the current study, manometry alone did not predict new onset dysphagia irrespective of whether a liquid or viscous bolus was used. Also, the current and previous study [6] have shown that if only intraluminal impedance is evaluated, this fails to predict post-operative dysphagia even with use of a viscous bolus.

The use of AIM in this study made it possible to measure 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. 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. 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. Pre-operative testing in patients revealed this time interval was significantly shorter in those who developed dysphagia after surgery. This finding indicates, that for those who developed post-operative dysphagia, 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 pressurised to facilitate passage through the esophagus. This is a new paradigm for characterising 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 of how pre-operative spatio-temporal relationships between esophageal pressure and bolus movement relate to post-operative dysphagia. Montenovo et al utilised impedance/manometry, while Scheffer et al used high-resolution EGJ manometry with fluoroscopy; both failed to find any pre-operative measures of pressure and flow through the esophagus and the EGJ that relate to post-fundoplication 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.

The new pressure-flow variables of this study were identified through the application of AIM analysis, using 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 evaluation of pharyngeal swallowing, which derived a measure of pharyngeal swallow effectiveness and risk for aspiration [11, 12]. The esophageal AIM analysis method uses a similar iterative analysis approach to examine a range of pressure-flow variables for potential associations with dysphagia. AIM analysis with DRI calculation pre-operatively 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 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, low-moderate grade dysphagia was experienced by patients after both types of fundoplication despite technically efficacious surgery, and yet in this setting DRI carried high prognostic value for predicting post-fundoplication dysphagia. This suggests that DRI is a sensitive instrument and also suggests it is not the data resolution (high or low) that is critical, but rather the relativity of data (impedance relative to pressure) that is critical for recognition of dysphagia risk. The implications are that AIM analysis
techniques could be clinically useful when applied to data of either low- or high-resolution acquisition systems for impedance/ manometry currently in use in many centres.

In our study pre-operative viscous bolus IBP, IBP slope and TNadImp-PeakP were significantly associated with dysphagia after fundoplication. Pre-operatively, these parameters for liquid swallows show a similar trend for pre-operative dysphagia. These parameters recorded post-operatively show a similar trend for post-operative dysphagia. The trends indicate further studies are warranted and it is likely that greater patient numbers will overcome a possible type II error. In support of this view, a comparison between our patients and healthy controls showed that patients with dysphagia pre-operatively 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 post-operative dysphagia. Future studies with AIM analysis might reveal how variations of operative technique such as length and diameter of the intraluminal esophago-fundal wrap may influence the onset of dysphagia after surgery.

That the most significant findings in this study were for viscous swallows highlights the fact that liquid and viscous boluses flow into and 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 while 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. Whilst 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. The spatial resolution of impedance/manometry sampling that we used for the current study has now been enhanced by high-resolution impedance/manometry. 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 demonstrated 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 that better describe the time-relevant relationships between bolus movement and esophageal pressure generation. This contrasts with separate analyses of bolus flow and luminal pressures. 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 measures variables that are impractical to derive through manual analysis and vastly reduces the time required for analysis.

In conclusion, we present novel findings from esophageal AIM analysis that indicate a patient’s individual risk of developing post-fundoplication dysphagia can be assessed prior to surgery. Future studies with high-resolution impedance/manometry are needed to further validate and calibrate this innovation.
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Table 1. Impedance parameters using conventional analysis before and after fundoplication

<table>
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<tr>
<th>ESOPHAGEAL FLOW</th>
<th>Liquid bolus N = 19</th>
<th>Viscous bolus N = 19</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-Op</td>
<td>Post-Op</td>
<td>P-value</td>
</tr>
<tr>
<td>Bolus presence time, s†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at 20 cm</td>
<td>2.1 (1.6, 2.5)</td>
<td>2.9 (1.9, 5.1)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>at 15 cm</td>
<td>3.0 (2.3, 3.5)</td>
<td>4.4 (3.6, 6.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>at 10 cm</td>
<td>3.9 (3.6, 4.4)</td>
<td>6.0 (4.6, 7.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>at 5cm</td>
<td>5.0 (4.4, 5.8)</td>
<td>7.1 (6.0, 8.7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Total bolus transit time, s</td>
<td>5.5 (4.8, 6.5)</td>
<td>8.0 (7.0, 9.6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Complete bolus clearance (%)*</td>
<td>100 (90, 100)</td>
<td>80 (55, 90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Abnormal bolus clearance (%)*</td>
<td>0 (0, 10)</td>
<td>20 (10, 45)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

†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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Liquid bolus  N = 19</th>
<th>P-value</th>
<th>Viscous bolus  N = 19</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DISTAL ESOPHAGEAL</strong>*</td>
<td>Pre-Op</td>
<td>Post-Op</td>
<td>Pre-Op</td>
<td>Post-Op</td>
</tr>
<tr>
<td>PeakP, mmHg</td>
<td>52 ± 5</td>
<td>61 ± 7</td>
<td>0.16</td>
<td>45 ± 4</td>
</tr>
<tr>
<td>PNadImp, mmHg</td>
<td>6 (3, 7)</td>
<td>6 (4, 10)</td>
<td>0.29</td>
<td>5 (4, 8)</td>
</tr>
<tr>
<td>IBP, mmHg</td>
<td>6 ± 1</td>
<td>11 ± 2</td>
<td>0.10</td>
<td>10 ± 2</td>
</tr>
<tr>
<td>IBP Slope, mmHg s(^{-1})</td>
<td>2 (1, 5)</td>
<td>4 (1, 19)</td>
<td>0.21</td>
<td>7 ± 1</td>
</tr>
<tr>
<td>TNadImp-PeakP</td>
<td>2.7 ± 0.3</td>
<td>3.1 ± 0.3</td>
<td>0.15</td>
<td>2.9 ± 0.3</td>
</tr>
<tr>
<td><strong>EGJ pressure during 10 sec prior to swallowing</strong></td>
<td>Pre-Op</td>
<td>Post-Op</td>
<td>Pre-Op</td>
<td>Post-Op</td>
</tr>
<tr>
<td>Basal EGJ pressure, mmHg</td>
<td>7 (4, 15)</td>
<td>17 (9, 27)</td>
<td><strong>0.01</strong></td>
<td>8 ± 2</td>
</tr>
</tbody>
</table>

*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 & after surgery were compared using Wilcoxon signed-ranks test or paired t-test.
Table 3. Viscous bolus swallow data before and after surgery by dysphagia status after surgery

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre Op Viscous Bolus N = 19</th>
<th>P-value</th>
<th>Post Op Viscous Bolus N = 19</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESOPHAGEAL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Dysphagia Post Op</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak P, mmHg</td>
<td>44 (40, 52)</td>
<td>0.45</td>
<td>68 ± 5</td>
<td>0.011</td>
</tr>
<tr>
<td>PNadImp, mmHg</td>
<td>11 (6, 13)</td>
<td>0.29</td>
<td>6 (3, 11)</td>
<td>0.06</td>
</tr>
<tr>
<td>IBP, mmHg</td>
<td>10 (7, 13)</td>
<td>0.032</td>
<td>10 ± 1</td>
<td>0.17</td>
</tr>
<tr>
<td>Distal_IBP, mmHg</td>
<td>3 (-2, 7)</td>
<td>0.08</td>
<td>9 ± 2</td>
<td>0.24</td>
</tr>
<tr>
<td>Distal_IBP Slope, mmHg/s</td>
<td>2 ± 1</td>
<td>0.048</td>
<td>8 ± 2</td>
<td>0.77</td>
</tr>
<tr>
<td>Distal_TNadImp-PeakP, s</td>
<td>4.0 ± 0.3</td>
<td>0.027</td>
<td>3.2 ± 0.7</td>
<td>0.13</td>
</tr>
<tr>
<td>Dysphagia Risk Index</td>
<td>9 (-2, 19)</td>
<td>0.014</td>
<td>33 (8, 61)</td>
<td>0.47</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Viscous bolus data BEFORE surgery</th>
<th>Healthy Control Subjects $N = 24$</th>
<th>No Dysphagia Pre or Post Op $N = 4$</th>
<th>Dysphagia Pre &amp; Post Op $N = 8$</th>
<th>Dysphagia Post Op only $N = 7$</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBP, mmHg</td>
<td>6 (4, 7)</td>
<td>10 (7, 13)</td>
<td>19 (12, 26)$^\wedge$</td>
<td>16 (12, 30)$^\wedge$</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Distal_IBP Slope, mmHg s$^{-1}$</td>
<td>4 (3, 7)</td>
<td>3 (-1, 4)</td>
<td>7 (3, 10)</td>
<td>5 (5, 14)$^*^\wedge$</td>
<td>0.022</td>
</tr>
<tr>
<td>Distal_TNadImp-PeakP, s</td>
<td>3.7 ± 0.1</td>
<td>4.0 ± 0.3</td>
<td>2.7 ± 0.4$^\wedge$</td>
<td>2.4 ± 0.4$^\wedge$</td>
<td>0.002</td>
</tr>
<tr>
<td>Dysphagia Risk Index (DRI)</td>
<td>6 (3, 13)</td>
<td>6 (-2, 19)</td>
<td>40 (16, 97)$^\wedge$</td>
<td>94 (23, 600)$^{**}$</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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 analysis of variance on ranks or one-way analysis of variance, 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 LEGENDS

Figure 1. Calculation of pressure-flow variables. A colour 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 & D) that defined: time between nadir impedance and peak pressure (tNadImp-PeakP), pressure at nadir impedance (PNadImp), peak pressure (PeakP) (C), median intra-bolus pressure (IBP) and IBP slope (D).
Figure 2. Composite dysphagia scores before and after fundoplication.
Figure 3. Pre-operative median Dysphagia Risk Index (DRI) according to the presence or absence of post-operative dysphagia.
Figure 4. 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 5. Images from AIM analysis of pre-operative viscous bolus swallows with colour 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 dash-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 pre-operatively the mean DRI = 16 (low). This contrasts with an image for (B) a patient with new-onset dysphagia after surgery in which pre-operatively 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 bolus movement present before surgery in a patient who developed dysphagia after fundoplication.
CONFLICT OF INTEREST/ STUDY SUPPORT

Guarantor of the article: Taher Omari, PhD, senior author and corresponding author.

The Corresponding Author on behalf of all authors accepts responsibility for the conduct of the study; has access to the study data; and acts for all authors regarding the decision to publish.

Specific author contributions:

Jennifer C Myers: study concept & design; subject recruitment; collection, analysis and interpretation of data; technical support; statistical analysis; drafting of manuscript, critical revision of manuscript and approval of final version.

Nam Q Nguyen: conventional impedance/manometry study design; conventional analysis and interpretation of data; critical revision of manuscript and approval of final version of manuscript.

Glyn G Jamieson: consultant surgical input; critical revision of manuscript and approval of final version.

Julia E Van’t Hek: data analysis; statistical analysis and approval of final version of manuscript.

Katrina Ching: collection and conventional analysis of data; technical support; approval of final version of manuscript.

Richard H Holloway: conventional impedance/manometry study design; critical revision of manuscript and approval of final version of manuscript.

John Dent: interpretation of data; drafting of manuscript, critical revision of manuscript and approval of final version.

Taher I Omari: automated analysis concept & design, development of analysis algorithms; data iteration, statistical analysis and interpretation of data; drafting of manuscript, critical revision of manuscript and approval of final version.

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REFERENCES


