



A Study of Dysphagia Symptoms and Esophageal Body Function in Children Undergoing Anti-Reflux Surgery

Journal:	<i>United European Gastroenterology Journal</i>
Manuscript ID:	UEG-17-0386
Manuscript Type:	Original Article
Date Submitted by the Author:	13-Nov-2017
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Keywords:	gastroesophageal reflux, fundoplication, dysphagia, diagnosis, high resolution manometry, impedance
Abstract:	<p>Background & Aims: The role of high resolution esophageal impedance manometry (HRIM) for establishing risk for dysphagia after anti-reflux surgery is unclear. We conducted a prospective study of children with primary GER disease, for whom symptoms of dysphagia to solids were determined pre- and post-operatively and we examined for features that may predict post-operative dysphagia.</p> <p>Methods: Thirteen children (aged 6.8 – 15.5 years) undergoing work up prior to 360° Nissen fundoplication were included. A dysphagia score assessed symptoms. A HRIM procedure recorded 5ml liquid, 5ml viscous and 2cm solid boluses. We assessed esophageal motility, esophago-gastric junction (EGJ) morphology, EGJ contractility and pressure-flow variables indicative of bolus distension pressures and bolus clearance pressures. A composite pressure-flow-index score (PFI) was also derived.</p> <p>Results: Pre-operative PFI was positively correlated with post-operative dysphagia score (PFI viscous bolus $r = 0.771$, $p < 0.005$). Of three variables</p>

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	that comprise the PFI, the ramp pressure measured during bolus clearance was the main driver of the effect seen (viscous bolus $r = 0.819$, $p < 0.005$). Conclusions: In order to mitigate symptoms in relation to anti-reflux surgery, dysphagia symptoms and esophageal function need to be pre-operatively assessed. In patients with normal motility, an elevated clearance pressure (indicating a pressure increase during luminal closure), may predict post-operative dysphagia.

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A Study of Dysphagia Symptoms and Esophageal Body Function in Children Undergoing Anti-Reflux Surgery

Short title: Dysphagia and Anti-Reflux Surgery

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Grant Support: T Omari, National Health & Medical Research Council Senior Research Fellowship. T Omari, Women's & Children's Hospital Research Foundation.

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Disclosures: T Omari, Inventorship of Australian Patent 2011301768 which covers the analytical methods described. All other authors have no conflicts of interest to disclose.

Author Contributions: T.O. study concept and design; analysis and interpretation of data; drafting of the manuscript. F.C. critical revision of the manuscript for important intellectual content. L.M. and L.F. acquisition of data; critical revision of the manuscript for important intellectual content. S.E. analysis of data critical revision of the manuscript for important intellectual content. G.D, R.A-A., S.K. and D.M. study concept and design; critical revision of the manuscript for important intellectual content.

Abbreviations: HRIM, high resolution impedance manometry; GER, gastroesophageal reflux; EGJ, esophago-gastric junction; LES, lower esophageal sphincter; CD, crural diaphragm; TZ, transition zone; CDP, contractile deceleration point; pH-MII, pH with multichannel intraluminal impedance; PPI, proton pump inhibitor; EPT, esophageal pressure topography; IRP4s, 4s integrated relaxation pressure; CFV, contractile front velocity; DCI, distal contractile integral; DL, distal latency; EGJ-CI, EGJ contractile index; DPA, distension pressure during bolus accommodation; DPCT, distension pressure during compartmentalized transport; DPE, distension pressure during esophageal emptying; PFI, pressure-flow-index; IR, impedance ratio; SDL, swallow to distension latency; DCL, distension to contraction latency; RP, ramp pressure; IEM, ineffective esophageal motility; EoE, eosinophilic esophagitis.

Acknowledgements: We thank Mrs G Seiboth, Mrs K Lowe and Ms S Kritas for assistance with performance of HRIM studies and Dr Junko Fujino for assistance with reviewing endoscopy images.

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Key Summary

1. The established knowledge on this subject
- The ability to accurately predict post-operative dysphagia risk is of interest to gastroenterologists. ‘Pressure-flow’ anomalies may be predictors of dysphagia symptoms following anti-reflux surgery.
 - Past studies were performed using ‘low-resolution’ perfusion lower esophageal sphincter sleeve-manometry.
2. What are the significant and/or new findings of this study?
- Dysphagia symptoms were common in our pediatric GER disease patients who were receiving diagnostic work up for anti-reflux surgery.
 - Of all parameters evaluated, bolus ‘clearing pressures’ were most reliably associated with dysphagia symptoms.

Abstract

Background: The role of high resolution esophageal impedance manometry (HRIM) for establishing risk for dysphagia after anti-reflux surgery is unclear. We conducted a prospective study of children with primary GER disease, for whom symptoms of dysphagia to solids were determined pre- and post-operatively and we examined for features that may predict post-operative dysphagia.

Methods: Thirteen children (aged 6.8 – 15.5 years) undergoing work up prior to 360° Nissen fundoplication were included. A dysphagia score assessed symptoms. A HRIM procedure recorded 5ml liquid, 5ml viscous and 2cm solid boluses. We assessed esophageal motility, esophago-gastric junction (EGJ) morphology, EGJ contractility and pressure-flow variables indicative of bolus distension pressures and bolus clearance pressures. A composite pressure-flow-index score was also derived.

Results: Pre-operative pressure-flow index was positively correlated with post-operative dysphagia score (viscous bolus $r = 0.771$, $p < 0.005$). Of three variables that comprise the pressure-flow index, the ramp pressure measured during bolus clearance was the main driver of the effect seen (viscous bolus $r = 0.819$, $p < 0.005$).

Conclusions: In order to mitigate symptoms in relation to anti-reflux surgery, dysphagia symptoms and esophageal function need to be pre-operatively assessed. In patients with normal motility, an elevated clearance pressure (indicating a pressure increase during luminal closure), may predict post-operative dysphagia.

Key Words: gastroesophageal reflux; fundoplication; dysphagia; diagnosis

Introduction

High resolution esophageal impedance manometry (HRIM) is now a widely available diagnostic paradigm offering the ability to record esophageal pressure and bolus flow with high fidelity. New objective biomechanical measures can be defined, which describe anatomical features, flow resistance and muscle contractility. These new characterizations of esophageal function may improve assessment, and may guide clinical decision making for esophageal motility disorders¹⁻³.

The HRIM technique may play a role in the assessment children with primary gastroesophageal reflux (GER) disease particularly for patients being considered for anti-reflux surgery⁴. By capturing bolus swallows pre-operatively, HRIM can characterize the dominant esophageal motor pattern and exclude a primary motor disorder, most importantly achalasia; which, while rare, may cause symptoms of regurgitation, heartburn, chest pain in addition to dysphagia⁵⁻¹². HRIM may also determine hypomotility^{3,9,10,13-16}, weak EGJ contractility^{9,16-24} and/or the anatomical separation of the lower esophageal sphincter (LES) from the crural diaphragm consistent with hiatus hernia subtype morphology^{3,20,25}. All of these features may be present in patients with primary GER disease.

The use of pre-operative HRIM assessments for establishing ‘risk’ for post-operative dysphagia has posed a significant challenge and its role is currently unclear. In pediatric series, post-operative dysphagia ranges from 12% - 40%^{26,27}. In some cases, dysphagia is intractable, with significant impact on quality of life. Dysphagia symptoms may mar a procedure that has been otherwise successful for reducing GER and may lead to a cascade of re-investigation and intervention. A reliable pre-operative test to identify patients with a high post-operative dysphagia risk is eagerly anticipated by clinicians and patients alike. The ability to accurately predict dysphagia risk would enable a more informed evaluation before proceeding to fundoplication, compared to other treatment options. To date we have published two reports suggesting that esophageal ‘pressure-flow’ anomalies, detectable during HRIM investigation, may be predictors of dysphagia

1 symptoms^{28,29}. This under-recognized esophageal dysfunction may be sub-clinical pre-operatively,
2 becoming relevant only when the EGJ is reconfigured. Alternatively the dysfunction may generate
3 symptoms of dysphagia pre-operatively which are unrecognized or being incorrectly attributed to
4 GER disease, rather than an esophageal motor disorder²⁸.
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11 Despite the encouraging results suggestive of predictors of dysphagia^{28,29}, these past studies were
12 performed using 'low-resolution' perfusion lower esophageal sphincter sleeve-manometry. This
13 methodology has dropped out of favor for routine use due to the advent of solid-state high
14 resolution manometry. We therefore conducted a new prospective case-series study of children with
15 primary GER disease undergoing fundoplication to examine for features that may predict post-
16 operative dysphagia. To do so, we employed current state-of-the art HRIM recording of pressure
17 and impedance patterns, performed *Chicago Classification* and derived pressure topography and
18 pressure-flow analytics to assess esophageal motor function. Symptoms of dysphagia to solids were
19 determined both pre-operatively and post-operatively, allowing at least six months for early
20 symptoms to resolve.
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Materials and Methods

Patients

Children under the management of the Departments of Gastroenterology and Surgery, Women’s and Children’s Hospital were prospectively enrolled. All children had symptoms of GER disease and were receiving pre-operative work up, having been referred for Nissen fundoplication surgery. The study was approved by the Human Ethics Committee of the Women’s and Children’s Hospital Adelaide (HREC No. 1855).

As part of routine pre-operative workup, patients also typically underwent 24 hour reflux monitoring by pH-only or pH with multichannel intraluminal impedance (pH-MII) probe, a barium swallow radiology study and upper GI endoscopy. Findings in relation to these tests, performed as an adjunct to HRIM, are reported based on medical record review. In order to fully exclude eosinophilic esophagitis (EoE) as the cause of dysphagia symptoms, all available biopsy specimens were scored for presence of eosinophils. EoE was defined as ≥ 15 eosinophils per high power field³⁰(eos/hpf).

Assessment of Dysphagia Symptoms

A dysphagia questionnaire modelled on the composite dysphagia score of Dakkak and Bennett³¹ was utilized. This *modified* Dakkak score assessed dysphagia for 9 different food types with increasing viscosity (water to meat; scale 0-45; score 11-45 indicates dysphagia to solids) and has been previously used in the context of pediatric dysphagia to document solid bolus hold up symptoms³².

Esophageal Function Testing

Esophageal motor function of all patients was assessed pre-operatively by HRIM. A 3.2mm diameter solid state catheter, incorporating 25 1cm-spaced pressure sensors and 12 adjoining

impedance segments, each of 2 cm, was used (Unisensor USA Inc, Portsmouth, NH). Pressure and impedance data were recorded at an acquisition rate of 20 samples per second (Solar GI acquisition system, MMS, The Netherlands).

Patients were intubated after application of topical anesthesia (2% lignocaine spray or gel) and studied sitting in the upright/semi-reclined posture. The catheter was positioned with sensors straddling the region from the proximal esophagus to the stomach. The standard protocol was 5-10 x 5ml test boluses of liquid (0.9% normal saline) and viscous ('EFT Viscous', Sandhill scientific) as well as 3-5 x 2cm solid (bread with added saline). The interval between consecutively administered boluses was >20sec.

Esophageal Pressure Topography Plot (EPT) Analysis

Esophageal motility disorders were diagnosed by Chicago Classification Version 3.0 (CC V3.0) based on the established hierarchical diagnostic algorithm³. Esophageal pressure topography (EPT) plots of bolus swallows were analyzed using semi-automated software (MMS Investigation & Diagnostic Software Version 9.3) and four established CC V3.0 EPT metrics were derived. These were; i) 4s integrated relaxation pressure of the esophago-gastric junction (IRP4s, mmHg), ii) contractile front velocity of the distal esophagus (CFV, cm/s), iii) distal contractile integral (DCI, mmHg cm/s) and iv) distal latency (DL, s)^{3,33}.

EGJ Dysfunction and Morphology

EGJ barrier function was manometrically assessed through calculation of the EGJ contractile index (EGJ-CI) and assessment of EGJ-crural diaphragm (CD) separation consistent with hiatus hernia. EGJ CI reflects the contractility of the EGJ over a period of three respiratory cycles. To determine EGJ CI, the margins of the EGJ were enclosed in a DCI box of three consecutive respiratory cycle's duration. The EGJ-CI (mmHg.cm) was determined as DCI value in mmHg.s.cm divided by the duration in seconds^{22,24}. Presence of hiatus hernia was determined by a visible separation of the LES

and CD pressure peaks at rest. EGJ morphology was defined as Type I (no LES-CD separation), Type II (partial separation) or Type III (full separation)³.

Esophageal Pressure-flow Analysis

Automated analysis (Figure 1) was applied to each swallow using purpose built software (*Esophageal AIMplot*, copyright T Omari) programmed in MatLab (The MathWorks Inc, Natick, MA, USA). Data based on *AIMplot* software algorithms have been previously published^{28,32,34-40}. However, for this work, the software underwent substantial revision to improve reliability, with focus on variables that have demonstrated most relevance in these past studies.

Following uploading of swallow data in comma separated values format (.csv), the analyst selected five key temporal and anatomical landmarks from a pressure topography plot; i) swallow onset, ii) esophageal proximal margin, iii) transition zone, iv) crural diaphragm and v) stomach. A separate pressure topography plot was then generated, upon which superimposed lines showed the timing and positions of the nadir impedance (indicating peak luminal distension) and the esophageal body contractile peak. The user then fine-tuned the landmarks paying particular attention to the region around contractile deceleration point (CDP) and the crural diaphragm position.

Four classes of pressure-flow variable were then algorithmically derived; these are described below and in Figure 1:

1. *Intra-bolus distension pressure* during bolus transport was determined as the pressure at nadir impedance. The average distension pressure (DP) was calculated for three anatomical regions approximating the different phases of bolus transport. These were *DP during bolus accommodation* (DPA, pressures UES to TZ), *DP during compartmentalized transport* (DPCT, pressures TZ to CDP) and *DP during esophageal emptying* (DPE, pressures from CDP to CD; see Figure 1B).

2. *Bolus clearance* was determined for the esophageal body from TZ to CDP based on the *impedance ratio* (IR = nadir impedance divided by the impedance measured at the contractile peak). A higher IR indicates *less* effective bolus clearance (see Figure 1C)⁴¹.

3. *Bolus flow latencies* were determined based on the pressure and impedance recording at the CDP level. These were the *swallow to distension latency* (SDL) from swallow to nadir impedance and *distension to contraction latency* (DCL) from nadir impedance to luminal clearance point. Luminal clearance was defined by the 50% recovery of impedance relative to baseline (see Figure 1C) this criterion for luminal clearance/closure has been previously validated and is in widespread use.^{42,43}

4. *Pressures generation during bolus clearance (or clearance pressures)* were measured over time from nadir impedance to luminal closure within the distal esophagus (25% of TZ to CDP length). The *closure pressure* (CP) was defined as pressure measured at the time of luminal closure (50% recovery of impedance relative to baseline) and the *ramp pressure* (RP) was determined by the mean gradient of pressure change over time during closure (Figure 1C). Note RP has also been called *IBP slope* in past publications^{28,29}.

The *pressure-flow index* (PFI) is a composite score derived by combining distension pressure, ramp pressure and flow latency variables using the following formula: $PFI = (DPE \cdot RP) / DCL$

Bolus Flow Time

Trans-EGJ *bolus flow time* (BFT) was estimated based on the method of Lin⁴⁴. BFT uses three impedance and three manometry signals through the EGJ with the distal impedance and pressure signals aligned with crural diaphragm contractions. Using the impedance signals, the duration of bolus presence (called *Bolus Presence Time*, BPT) was determined (onset of bolus presence defined by impedance drop to 90% of the nadir; offset defined as the return to 50% of the impedance baseline). Using the manometry signals the flow-permissive pressure gradient periods (i.e. esophageal pressure > crural and gastric pressure) within to the overall period of bolus presence

were identified. BFT was defined by the sum of the flow permissive pressure gradient periods. A shorter BFT is indicative of a reduced period of esophageal emptying^{37,44}.

Post-Operative Assessments

The families of patients were contacted post-operatively (>6 months) and dysphagia symptoms were re-assessed. Patients were also invited to repeat HRIM. A further medical record review was undertaken at follow up to determine current proton pump inhibitor (PPI) use and other post-operative investigations as an indication of symptom recurrence.

Statistical Analysis

Statistical analysis was performed using SPSS Statistics 23 (IBM Corporation, USA). Data are expressed as means (standard deviation) if normally distributed (passed Shapiro-Wilk normality testing) or otherwise median [interquartile range]. Spearman’s correlation rho was used to investigate relationships between continuous variables and dysphagia scores. Grouped comparisons were performed using t-test or Mann-Whitney U test. To compare pre- vs. post-operative findings across consistencies, repeated measures ANOVA was performed using General Linear Modelling with time point and bolus type conditions as repeated measures; data failing Shapiro-Wilk normality was normalized by logarithmic transformation. Receiver operator curve analysis was performed to determine if larger values of the pressure-flow index score indicated stronger evidence for a dysphagia; ROC curve area, sensitivity and specificity were determined. Only p-values ≤ 0.099 are reported.

Results

Patients

Children with a diagnosis of primary GER disease who underwent HRIM investigation as part of pre-operative work up for full 360° wrap Nissen fundoplication surgery were included in this study. Twenty seven children aged 0.8-16.1 years were originally identified. However, nine children were excluded due to absence of a reliable pre-operative assessment of dysphagia symptoms by modified Dakkak questionnaire. Two children were excluded because at the time of analysis they not undergo surgery. A further three children were excluded due to a poor quality HRIM recording; two children, both aged 1 year, were unsettled during the procedure rendering the measurement uninterpretable and one child, aged 16 years, was not able to complete the swallow protocol. The final dataset included 13 children aged 6.8-15.5 years (average 12.5 years) who had undergone surgery and had completed pre- and post-operative assessments of dysphagia symptoms by modified Dakkak questionnaire. Seven of these patients agreed to undergo post-operative HRIM investigations.

Pre-Operative Clinical Findings

The relevant clinical data for the 13 included patients are shown in Table 1. Most patients had a reported clinical history of typical symptoms of heartburn and/or regurgitation. Eleven had one or more abnormal finding on 24 hour pH-MII probe (abnormal reflux index, abnormal reflux frequency and/or positive symptom association probability) and three showed endoscopic esophagitis. None of the patients showed macroscopic signs of EoE, eosinophil counts in biopsy specimens ranged 0-5 eos/hpf thus none met the established clinical definition of EoE (≥ 15 eos/hpf). Seven patients were radiologically investigated by barium swallow and all were reported to have normal esophageal bolus transit. EGJ barrier dysfunction on HRIM was apparent in six of the patients, of whom one had evidence of hiatus hernia (partial LES-CD separation consistent with

a Type 2 EGJ Morphology). Two patients had evidence of esophageal body contractile weakness consistent with a CC V3.0 diagnosis of *ineffective esophageal motility* (IEM)³. Five patients were on PPI therapy when followed up post-operatively (Table 1).

[Table 1 here]

Pre-Operative Dysphagia Questionnaire

Pre-operative Dakkak dysphagia scores for all participants can be seen in Table 1, eight children returned a pre-operative Dakkak score >10 indicative of pre-operative dysphagia to solids. During liquid swallows, higher proximal distension pressure (DPA) and longer bolus flow time (BFT) correlated with greater pre-operative Dakkak scores (Table 2). However, neither parameter was significantly different based on grouped analyses comparing those patients with and without pre-operative dysphagia. Pre-operative EGJ-CI did not correlate with pre-operative Dakkak scores ($r = 0.463$, ns), however was the only other parameter to be associated with pre-operative dysphagia on grouped analysis being higher in patients reporting dysphagia (dysphagia 30.9 (15.1) mmHg.cm vs. no dysphagia 13.3 (11.9) mmHg.cm, $t = 2.201$, $p=0.050$).

[Table 2 here]

Post-Operative Dysphagia Questionnaire

Five of the eight patients with pre-operative dysphagia improved post-operatively with fundoplication surgery decreasing their Dakkak scores to <10 (Table 1). However, four patients reported significant dysphagia post-operatively; three with persisting dysphagia and one with ‘new’ dysphagia (14 year old boy with Dakkak 0 pre-operatively increasing to Dakkak 18 post-operatively).

Six patients were investigated by 24 hour pH/pH-MII probe after the surgery on clinical grounds due to symptom recurrence. This showed that the surgery was highly effective in reducing esophageal acid exposure, even though symptoms were refractory (Figure 2). These patients had significantly greater dysphagia post-operatively than those without refractory symptoms (Dakkak 13[8, 23] in refractory patients vs. 0[0, 2.2] in other patients, $t = 3.095$, $p = 0.001$), suggesting that post-operative dysphagia symptoms may have been a contributor underlying the post-operative investigations.

Pre-Operative Findings Associated with Symptoms of Post-Operative Dysphagia

All patients were symptomatic for GER disease and findings from routine reflux monitoring, upper GI endoscopy and barium radiology investigations did not discriminate the patients with post-operative dysphagia. However, manometric features that would normally corroborate a diagnosis of primary GER disease; such as evidence of IEM or EGJ barrier dysfunction were *never* seen in the patients reporting post-operative dysphagia (Table 1).

Of the parameters measured pre-operatively, higher ramp pressure, closure pressure and pressure-flow index were most significantly correlated with post-operative Dakkak score and, for all of these variables, correlations based on viscous swallows were superior (Table 3). Grouped analysis based on patients with and without post-operative dysphagia also showed that pre-operative viscous bolus clearance pressures were higher in those who had post-operative dysphagia compared to those who did not have post-operative dysphagia (RP 47 [27, 71] mmHg/s vs. 13 [10, 18] mmHg/s respectively, $p = 0.002$ and CP 72 [48, 100] mmHg vs. 31 [25, 38] mmHg respectively, $p = 0.002$). Consistent with the findings in relation to pre-operative dysphagia, BFT was longer pre-operatively (Table 3) in patients with post-operative dysphagia compared to those without dysphagia (liquid BFT 3.29(0.98) sec vs. 1.95(0.98) sec respectively, $p = 0.045$ and viscous BFT 1.48(0.80) vs. 2.58 (0.27) sec respectively, $p = 0.025$). Pre-operative EGJ-CI did not correlate with post-operative Dakkak scores ($r = 0.119$, ns).

[Table 3 here]

In order to help clarify and explain our main results in relation to post-operative dysphagia we provide two case examples that are illustrative of these findings:

Case 1: A child with pre-operative dysphagia that resolved (Figure 3 A-D)

A 9 year old female with symptoms of regurgitation and vomiting who had evidence of esophagitis on endoscopy and a positive symptom association to heartburn symptoms on pH-MII study. Pre-operative HRIM showed minor evidence of distal pressure compartmentalization, however esophageal motility was considered normal (no hiatus hernia, EGJ-CI 43 mmHg.cm, mean liquid DCI 1960 mmHg.cm.s and IRP4s 12 mmHg). The patient reported dysphagia to solids pre-operatively (Dakkak 20) which resolved following fundoplication (Dakkak 0). The patient was considered to be successfully treated without symptom recurrence.

Case 2: A child with pre-operative dysphagia that did not resolve (Figure 3 E H)

A 16 year old female with symptoms of regurgitation and vomiting who was endoscopy normal but had abnormal esophageal acid exposure (reflux index 19.2%) and positive symptom association to regurgitation symptoms on 24 hour pH-MII study. Pre-operative HRIM showed no evidence of distal pressure compartmentalization and esophageal motility was considered normal (No hiatus hernia, EGJ-CI 32 mmHg.cm, mean liquid DCI 2541 mmHg.cm.s, IRP4s 10 mmHg). The patient reported significant dysphagia pre-operatively (Dakkak 41.5) which *did not* resolve following fundoplication (Dakkak 39.5). Repeat pH-MII probe demonstrated normalization of reflux parameters.

When the pressure-flow analysis data derived for Case 1 and Case 2 were compared (Figure 3) there were striking differences in relation to the clearance pressures (CP and RP) which were much higher pre-operatively for the viscous swallows in Case 2 (Figure 3 I). In Case 2, luminal closure

occurred much *later* in time (compare Panel B vs. Panel F in Figure 3) and a pattern of pressure increase with diameter decrease, known as *auxotonic contraction*, was observed (Figure 3 H).

Effects of Surgery on Biomechanical Measures

Data were complete for liquid and viscous boluses only from the seven patients who agreed to undergo repeat post-operative HRIM. The main effects of fundoplication surgery accounting for bolus consistency were investigated by repeated measures ANOVA. Despite the small sample size a number of anticipated trends were revealed (Table 4), most importantly an increase in distension pressures in the distal esophagus and EGJ (higher DPE and IRP4) consistent with surgery increasing esophageal emptying resistance. Other effects included lower proximal distension pressures (DPA), suggesting improved proximal flow resistance, and a delay in the timing of maximum bolus distension of the distal esophagus after swallows (longer SDL). The pressure-flow index, which includes DPE in its calculation, was higher post-operatively. The esophageal clearance pressures (RP and CP) which were strongly associated with post-operative dysphagia overall (Table 3), were not altered by surgery. EGJ CI, indicative of EGJ tone, was significantly increased by surgery ($t = 5.595$, $p = 0.001$).

[Table 4 here]

Discussion

Dysphagia symptoms and esophageal body function were investigated in children with GER disease undergoing Nissen fundoplication surgery. The main findings of our study were; i) patients frequently reported symptoms of dysphagia to solids pre-operatively, ii) fundoplication surgery decreased dysphagia symptoms in most patients, however, one third of patients had post-operative dysphagia and, iii) these patients, with refractory or new dysphagia were distinguishable pre-operatively by the presence of elevated bolus clearing pressures.

When assessed pre-operatively, bolus hold up symptoms to solids were common and improved following surgery. This suggests that primary GER disease was very likely to be a causal factor underlying bolus hold up symptoms in most patients. The fact that few individual parameters appeared to link to pre-operative dysphagia is consistent with the multifactorial nature of the mechanisms that may underlie symptom generation in the pre-operative setting; i.e. before reflux as an influencer of symptoms is mitigated. Our study also identified four patients in whom dysphagia persisted or developed as a new symptom. In these patents, manometry-based evidence to further corroborate primary GER disease diagnosis was absent; i.e. none of these patients had a low EGJ CI, none with EGJ morphology consistent with hiatus hernia and none demonstrating an IEM subtype. Our findings support a recent adult series showing EGJ-CI has clinical utility in assessing EGJ barrier function at baseline and after surgery²².

In the current study, the pre-operative clearing pressures, namely ramp pressure and closure pressure, demonstrated the strongest correlations with post-operative dysphagia symptom scores. This is not a new observation; associations of clearing pressures and bolus hold up perception have been previously reported in the context of post-operative dysphagia^{28,29} and non-obstructive dysphagia^{2,45-47} (note, in these previous studies clearing pressures were defined by the parameter ‘IBP slope’). A consistent observation of the current and past studies was that the correlation of greater symptoms with higher clearance pressures was most apparent when the heavier viscous and

solid bolus consistencies were swallowed. Interestingly, in the subgroup of patients for whom pre- and post-operative HRIM data was available, fundoplication increased EGJ resistance but had little or no effect on clearance pressures. Bolus flow time, a parameter which is typically shorter in non-obstructive dysphagia³⁷ and achalasia^{48,49}, was paradoxically *longer* in relation to dysphagia in our study. Furthermore, the IRP4 parameter used to diagnose EGJ outflow obstruction was not associated with dysphagia. These findings suggest that obstructed esophageal emptying is not a causative factor for dysphagia within our study cohort. The most consistent data identifies higher clearance pressures (RP and CP) as being a relevant feature. Furthermore, the phenomenon of high clearance pressures appears to pre-exist surgery and, unlike known biomechanical markers of esophageal emptying resistance (i.e. DPE and IRP4) are not altered by surgery. The pressure-flow index composite score, being calculated based on a formula which includes both distension pressures (DPE) and clearance pressures (RP) was found to be increased by surgery and was also higher in relation to post-operative dysphagia. We remain hopeful that the derivation of the PFI may provide a useful clinical measure to distinguish pressure-flow abnormalities in the context of findings of otherwise 'normal' peristalsis. The optimal PFI cutoff criteria suggested by this study are provided in Table 5.

[Table 5 here]

In order to understand our observations we need to recognize that resistance to bolus flow during bolus transport occurs on a continuum with normal un-impeded flow at one extreme and obstructed flow at the other extreme. Obstructed luminal flow can be deduced by the presence of high compartmentalized distension pressures (for example, in relation to focal strictures and EGJ outflow obstruction). However, if bolus flow is *impeded* rather than obstructed, then distension pressures may be less relevant. In relation to impeded flow, clearance pressures which quantify bolus pressurization superior to the bolus midpoint (i.e. towards and at the bolus tail) are important because they drive bolus movement. A high clearance pressure suggests that the contraction, rather than being *isometric* (pressure rise occurs with a closed lumen after the bolus has passed) is instead

auxotonic (pressure increases with a closing lumen as the bolus passes, see Figure 3 H)^{2,50,51}. The recording of *auxotonic* pressure-flow phenomena demonstrates that the demands placed on the esophageal muscles to do mechanical work (expend energy) during bolus clearance are greater. The most likely factor leading to auxotonic pressures is that the bolus is, for one or more reasons, ‘more reluctant’ to move along the esophageal lumen. Various factors that are both intrinsic and extrinsic to the swallowed bolus material influence how easily transportable by peristalsis the bolus will be. For example, the rheology (resistance to flow) of the swallowed material is important in this setting; solids resist flow and are associated with the highest clearing pressures³⁶. Additionally, there are other *superimposed* factors that are unrelated to bolus consistency but that may still be relevant. These include, i) the size of luminal aperture, ii) the stiffness of the esophageal wall and iii) the surface ‘tackiness’ of the mucosal lining due to the presence/absence of luminal secretions which influence surface-interaction and lubrication.

The mechanism(s) by which the rate of pressure change during the clearance phase of the bolus and/or the max pressure generated behind the bolus tail may directly lead to bolus perception are unclear. We assume that the relevant sensory afferent mechanisms are largely insensitive to the *isotonic* and *isometric* contractile states of the distal esophageal wall, as these are the most commonly encountered in health⁵⁰. However, the active tension produced in relation to a prolonged *auxotonic* contractile state may be different as generating sufficient additional wall tension to produce a noxious stimulus. In other words, we should assume that a bolus being transported that has been orally processed to be soft, moist and slippery (via saliva coating and mucosal secretions lining the esophagus all the way down) should not be felt. Conversely, a bolus that is hard, dry and resistive should be felt in order to generate alarm sensations that will alter eating behavior. However, in certain pathophysiological situations, a usually soft, moist and slippery bolus may be rendered less easy to transport. If so, this will lead to the bolus being felt because its transport is being impeded and the contractile state of the esophageal muscle has ‘switched’ from normal to

1 abnormal. Despite these altered circumstances the bolus may still be fully transported into the
2 stomach.
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6 The elevated clearance pressures seen in relation to dysphagia may be a sign that esophageal bolus
7 transport has become dysregulated due to an enteric nervous system (ENS) and/or a muscle
8 dysfunction. It is known, for example, that EoE causes dysphagia symptoms due to associated wall
9 thickening, stiffness and motility abnormalities^{30,52-54}. While none of the patients enrolled in the
10 current study were characterized with EoE, we cannot fully discount other changes to the circular
11 and longitudinal muscle. Neurally mediated relaxation and contraction of the esophageal muscle
12 ahead of and then behind the moving bolus is important for normal bolus transport and dependent
13 upon normal functioning of the ENS^{55,56}. Multiple rapid swallowing, a test to reveal aberrant ENS
14 inhibition, has been reported to predict post-operative dysphagia⁵⁷ and sustained esophageal
15 distension may reveal abnormal spontaneous motor patterns in dysphagic patients with otherwise
16 normal primary peristalsis⁵⁸. The contractile decoupling of the circular and longitudinal muscle
17 layers may also be highly relevant to our observations, whereby selective longitudinal muscle
18 contractile dysfunction has been reported in various disorders⁵⁹ and it has been proposed that this
19 de-coupling of the muscle layers during peristalsis could potentially perturb the normal ability of
20 the esophagus to biomechanically distend⁵⁹. That is, a motor pattern suggestive of impaired
21 descending inhibition may manifest because of contractile decoupling, even though the inhibitory
22 apparatus is functioning normally. Irrespective of the underlying mechanism(s), the lack of ability
23 of the lumen to distend will impede normal bolus flow leading in turn to high clearance pressures
24 and (according to our hypothesis) heightened bolus perception.
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50 The strength of our study lies in the highly detailed characterization of symptoms, reflux, motility
51 and pressure-flow phenomena in a series of patients enrolled in a single center. Our data broadly
52 support the findings of two previous pre-post fundoplication studies^{28,29}, however we acknowledge
53 the need for a larger prospective study that takes advantage of these refined measurement and
54 analysis methods. As data from patients younger than six years of age were not included we caution
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against generalizing of our findings to younger pediatric GER disease patients. There are inherent challenges for generating the high quality data needed for the HRIM study to be meaningful for the type of analysis applied. For results to be reliable, children need to be able to tolerate the procedure and repeat-swallow viscous bolus consistencies on command. Investigations of infants and toddlers are the most challenging and the utility of our approach to investigate them pre-operatively was not tested.

In conclusion, our study demonstrates that both dysphagia symptoms and a finding of normal esophageal motility are common in pediatric GER disease patients receiving diagnostic work up for anti-reflux surgery. In order to avoid symptom recurrence and a potential cascade of re-investigations and interventions, dysphagia symptoms need to be correctly attributed to GER disease. In the absence of manometric evidence consistent with GER disease; such as IEM and a hypotensive or disrupted EGJ, then pressure-flow analytics may detect subtle abnormalities that may be symptom generating. Clearance pressures are quantifiable phenomena that may explain dysphagia symptoms and predict post-operative symptom emergence or recurrence in the context of otherwise normal esophageal motility. The underlying factors that may contribute to the finding of abnormal clearance pressures are unclear and will require further investigation.

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Figure Legends

Figure 1. Derivation of Pressure-Flow metrics. Automated analysis was applied to each swallow within a region of interested (see inset Clouse plot **lower right**). **A.** A pressure topography iso-contour plot with superimposed lines showing the position of the nadir impedance (thick purple line; indicating peak distension) and contractile peak (thick red line) over time. The analyst fine-adjusted the landmarks, paying particular attention to the transition zone (TZ), the contractile deceleration point (CDP; yellow star) and crural diaphragm (CD). **B. Intra-Bolus Distension Pressure** during bolus transport was determined by pressure at nadir impedance which was measured along the esophagus. The average distension pressure (DP) was determined within three anatomical regions approximating the different phases of bolus transport. These were accommodation (DPA, pressures proximal to TZ), compartmentalized transport (DPCT, pressures TZ to CDP) and esophageal emptying (DPE, pressures from CDP to CD). **C.** Effectiveness of *Bolus Clearance* was determined from TZ to CDP based on the impedance ratio ($IR = \text{nadir impedance} / \text{impedance at contractile peak}$). A higher IR equates to *less* effective bolus clearance. **C. Bolus Flow Latencies and Clearance Pressures** were determined based on the pressure and impedance recordings at the CDP level. Swallow to distension latency (SDL) was measured from swallow onset to nadir impedance and distension to contraction latency (DCL) from NI to luminal clearance/closure corresponding to recovery of impedance to 50% from baseline (**see plot lower left**). The ramp pressure (RP) was determined within the distal esophagus (sensors within distal 25% of the TZ to CDP length) and defined by the mean gradient of pressure change over time from maximum distension (NI) to luminal closure (**see plot lower middle**, note impedance presented relative to baseline and reversed in direction). Variables DCL, DPE and RP were combined to derive the pressure-flow index (PFI) composite score.

Figure 2. Reflux monitoring findings in six patients investigated by pH or pH-MII probe pre- and post-operatively due to symptom recurrence.

Wilcoxon Signed Rank Test standardized t and p-value shown. Total liquid GER data (in C) are incomplete for four patients due to pH-MII not being performed pre-operatively.

For Peer Review

Figure 3. Pre-operative recordings and pressure-flow data from example Cases: Case 1 with pre-operative dysphagia that resolved post-operatively and Case 2 with significant persisting dysphagia. Tracings are based on recordings of 5ml viscous bolus swallows. Panels **A and E** show esophageal pressure topography of the distal esophagus with axial location of contractile deceleration point (CDP) marked. **Panels B and F** show pressure (black) and impedance (purple) profiles over time at the level of the CDP. **Panels C and G** show the pressure (black) and the impedance *relative to baseline* (purple) for the period 1 s before to 0.5s after the 30mmHg iso-contour (the direction of impedance change is *reversed* compared to B and F; 100% is pre-swallow baseline, 0% is maximum distension and 50% defines luminal closure). Note that the impedance-defined luminal closure (50%) occurs relatively *later* in time for Case 2, resulting greater clearance pressures being generated as the lumen closes. **Panels D and H** show the relationship between relative impedance (x axis) and pressure (y axis) over time. As seen in D, from Case 1, the lumen opens and then closes without any change in clearance pressure (known as isotonic contraction). As seen in H, from Case 2, the lumen opens and then closes with clearance pressures increasing (known as auxotonic contraction). **I** shows bar charts of patient Dakkak scores and the average data for the relevant pressure-flow metrics derived for liquid and viscous bolus swallows. Note, markedly higher clearance pressures (RP and CP) for Case 2.

Age (yrs)	History & Symptoms	pH MII probe	Upper GI Endoscopy		Barium Radiology	HRM EGJ Barrier	HRM Motility	Post-Op Symptom Recurrence	Post-Op PPI Use	Modified Dakkak Score (maximum 45)		
			Esophagitis	Eosinophils per hpf						Pre-Op	Post-Op	Post-Op Dysphagia Sx.
14	AB	AR	NO	0	n/a	Hypo.	Nor.	YES	Off	0.0	8.0	None or mild (Dakkak 0-10)
13	HB, RV	AR	NO	0	n/a	Hypo.	Nor.	NO	Off	3.5	4.5	
14	RV	AR	NO	3	n/a	Hypo./HH	IEM	NO	On	7.0	0.0	
11	RV	AR	NO	0	n/a	Hypo.	Nor.	YES	Off	8.0	8.0	
12	HB, RV, RPPI	Nor.	NO	0	Nor.	Nor.	Nor.	NO	Off	10.5	0.0	
13	HB, RV	AR	YES	1	Nor.	Hypo.	IEM	NO	On	12.0	0.0	
14	HB, N	AR	NO	0	n/a	Hypo.	Nor.	NO	Off	13.5	0.0	
9	RV	+SA	YES	3	Nor.	Nor.	Nor.	NO	On	20.0	0.0	
12	Neuro, FT	AR	n/a	n/a	Nor.	Nor.	Nor.	NO	Off	29.0	4.5	New or Persisting (Dakkak > 10)
14	Dys	AR, +SA	NO	1	Nor.	Nor.	Nor.	YES	On	26.0	12.0	
7	RV	AR	NO	5	Nor.	Nor.	Nor.	YES	On	12.0	14.0	
14	RV	Nor.	YES	2	Nor.	Nor.	Nor.	YES	Off	0.0	18.0	
16	RV	AR, +SA	NO	1	n/a	Nor.	Nor.	YES	Off	41.5	39.5	

Table 1. Summary of clinical findings from thirteen children who received GER diagnostic work-up and complete HRIM protocol prior to receiving anti-reflux surgery and in whom long-term followed up to assess bolus hold up symptoms was achieved.

Modified Dakkak scores, which define bolus hold-up perception, are shown in the far right columns. The four patients reporting new or ongoing swallowing difficulties are ranked by their post-operative Dakkak score, other patients ranked by pre-operative Dakkak score.

Abbreviations: n/a – not available; Nor. – normal findings.

History: Neuro, Neurological patient; HB, heartburn; RV, regurgitation and/or vomiting; N, nausea; Dys, dysphagia; FT, failure to thrive; IC, irritability and crying; AB, acid brash; RPPI, refractory to PPI.

pH MII GER: AR, abnormal acid GER; NAR, abnormal non-acid GER; +SA, positive symptom association probability.

HRM: Hypo, hypotensive EGJ; HH, hiatus hernia morphology; IEM, ineffective esophageal motility.

	Metric vs. Pre-Op Dakkak Score		
Pre-Op Metric	LIQ	VIS	Solid
Esophageal Pressure Topography			
DCI	0.085	-0.028	0.069
CFV	-0.094	-0.240	0.118
DL	-0.247	-0.413	-0.198
IRP4s	-0.342	-0.455	0.273
Intrabolus Distension Pressures			
DPA	0.554(0.05)	0.336	0.047
DPCT	0.314	0.229	0.190
DPE	-0.008	0.160	0.248
Intrabolus Clearance Pressures			
RP	0.336	0.179	-0.212
CP	0.466	0.287	-0.402
Flow/Distension Timing			
SDL	0.074	-0.264	-0.259
DCL	-0.234	-0.163	-0.377
Composite Measures			
Pressure Flow Index	0.369	0.309	0.182
Impedance Ratio	0.094	0.163	-0.006
Bolus Flow Time	0.617*	-0.074	-0.524(0.066)
Table 2. Correlation esophageal function variables recorded pre-operatively with dysphagia symptoms reported pre-operatively. Spearman's correlation rho based on data from 13 patients with complete HRIM studies for all consistencies. *Indicates significant correlation (two tail; *p<0.05).			

	Metric vs. Post-Op Dakkak Score		
Pre-Op Metric	LIQ	VIS	Solid
Esophageal Pressure Topography			
DCI	0.402	0.445	0.465
CFV	0.235	0.173	0.060
DL	-0.270	-0.088	-0.150
IRP4s	0.235	0.204	0.235
Intrabolus Distension Pressures			
DPA	-0.167	0.249	0.221
DPCT	-0.040	-0.119	0.380
DCE	-0.028	-0.062	0.116
Intrabolus Clearance Pressures			
RP	0.230	0.819***	0.709**
CP	0.337	0.802***	0.261
Flow/Distension Timing			
SDL	-0.261	-0.023	-0.207
DCL	0.014	-0.145	-0.201
Composite Measures			
Pressure Flow Index	0.366	0.771***	0.757***
Impedance Ratio	-0.184	-0.028	0.028
Bolus Flow Time	0.584*	0.527(0.064)	0.068
Table 3. Correlation esophageal function variables recorded pre-operatively with dysphagia symptoms reported post-operatively. Spearman's correlation rho based on data from 13 patients with complete HRIM studies for all consistencies. *Indicates significant correlation (two tail; *p<0.05, **p<0.01, ***p<0.005).			

	Time Point		Main Effects RM-ANOVA	
Metric	Pre-Op Mean (CI)	Post-Op Mean (CI)	Surgery (F, p)	Consistency (F, p)
Esophageal Pressure Topography				
DCI mmHg.cm.s	1214 (643, 1784)	1102 (454, 1751)	-	-
CFV cm/s	3.8 (2.9, 4.7)	4.1 (2.2, 6.1)	-	-
DL s	6.8 (6.0, 7.6)	7.3 (5.9, 8.8)	-	↑F 3.919, p 0.095
IRP4s mmHg	9.0 (5.9, 12.1)	13.5 (7.7, 19.3)	↑F 4.811, p 0.071	-
Intrabolus Distension Pressures				
DPA mmHg	3.7 (1.1, 6.3)	0.4 (-1.2, 2.0)	↓F 6.233, p 0.047	↑F 33.488, p 0.001
DPCT mmHg	6.3 (2.6, 10.1)	7.1 (3.5, 10.7)	-	↑F 22.502, p 0.003
DPE mmHg	14.2 (8.8, 19.5)	19.9 (12.2, 27.6)	↑F 3.979, p 0.093	↑F 31.103, p 0.001
Intrabolus Clearance Pressures				
RP mmHg/s	19.0 (4.4, 33.6)	15.9 (8.4, 23.4)	-	↑F 7.526, p 0.034
CP mmHg	40.0 (21.6, 58.4)	38.1 (27.5, 48.8)	-	↑F 12.144, p 0.013
Flow/Distension Timing				
SDL s	3.9 (2.9, 4.8)	4.6 (3.2, 5.9)	↑F 5.797, p 0.053	↑F 13.298, p 0.011
DCL s	2.5 (1.9, 3.1)	1.6 (1.2, 1.9)	-	↓F 38.956, p 0.001
Composite Measures				
Pressure Flow Index	69.7 (25.5, 114.0)	428 (26.1, 830.8)	↑F 5.173, p 0.063	↑F 25.865, p 0.002
Impedance Ratio	0.29 (0.22, 0.37)	0.34 (0.27, 0.41)	-	↑F 27.932, p 0.001
Bolus Flow Time s	2.2 (1.2, 3.2)	2.0 (1.2, 2.7)	-	-

Table 4. Effect of fundoplication surgery on esophageal function variables. Data from seven patients participating in repeat study. Data are estimated marginal mean (95% Confidence interval of difference). Statistics for RM-ANOVA shown. Main effects in relation to surgery and bolus type on swallow function variables are indicated; ‘-’ indicates no effects; ↑↓ indicates the directionality of the effects.

ROC Parameters		Dakkak Score Used to Define Post-Operative Dysphagia		
		Dakkak >0	Dakkak >5	Dakkak >10
Patients Positive/Negative		8/5	6/7	4/9
ROC area (p-value)	Liquid	0.775 (ns)	0.667 (ns)	0.556 (ns)
	Viscous	0.950 (0.008)	0.857 (0.032)	0.833 (0.064)
	Solid	0.875 (0.028)	0.905 (0.015)	0.833 (0.064)
Optimal PFI cut-off (sens, spec)	Liquid	32 (0.75, 0.80)	32 (0.83, 0.74)	38 (0.75, 0.67)
	Viscous	151 (1.00, 0.80)	221 (0.83, 0.86)	280 (1.00, 0.78)
	Solid	1240 (0.75, 1.00)	1240 (0.83, 0.86)	1629 (0.75, 0.89)
Table 5. Prognostic value of the pressure-flow index score to predict levels of dysphagia. Receiver operator curve analysis determining if larger values of the PFI result indicate stronger evidence for a dysphagia.				

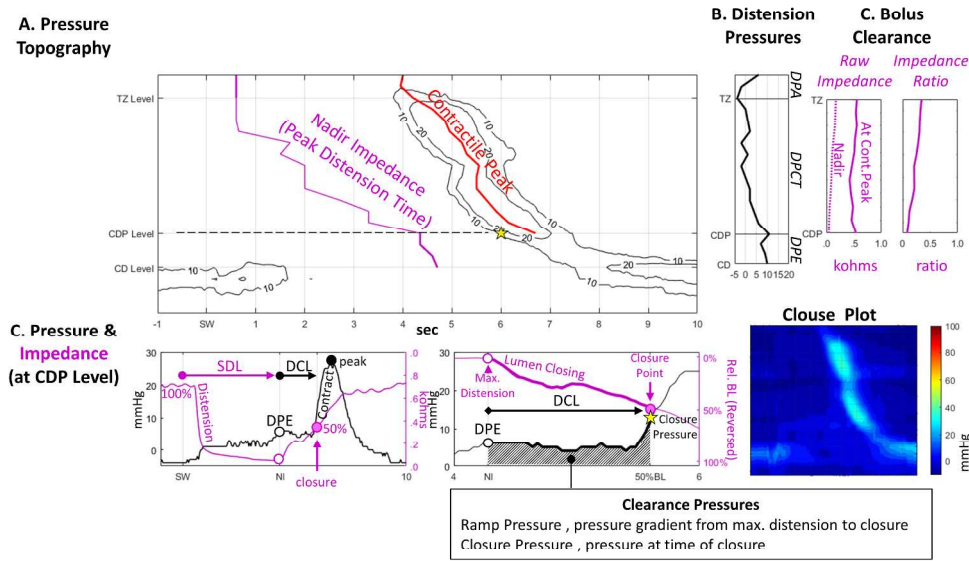


Figure 1. Derivation of Pressure-Flow metrics. Automated analysis was applied to each swallow within a region of interested (see inset Clouse plot lower right). A. A pressure topography iso-contour plot with superimposed lines showing the position of the nadir impedance (thick purple line; indicating peak distension) and contractile peak (thick red line) over time. The analyst fine-adjusted the landmarks, paying particular attention to the transition zone (TZ), the contractile deceleration point (CDP; yellow star) and crural diaphragm (CD). B. Intra-Bolus Distension Pressure during bolus transport was determined by pressure at nadir impedance which was measured along the esophagus. The average distension pressure (DP) was determined within three anatomical regions approximating the different phases of bolus transport. These were accommodation (DPA, pressures proximal to TZ), compartmentalized transport (DPCT, pressures TZ to CDP) and esophageal emptying (DPE, pressures from CDP to CD). C. Effectiveness of Bolus Clearance was determined from TZ to CDP based on the impedance ratio (IR = nadir impedance divided by impedance at contractile peak). A higher IR equates to less effective bolus clearance. C. Bolus Flow Latencies and Clearance Pressures were determined based on the pressure and impedance recordings at the CDP level. Swallow to distension latency (SDL) was measured from swallow onset to nadir impedance and distension to contraction latency (DCL) from NI to luminal clearance/closure corresponding to recovery of impedance to 50% from baseline (see plot lower left). The ramp pressure (RP) was determined within the distal esophagus (sensors within distal 25% of the TZ to CDP length) and defined by the mean gradient of pressure change over time from maximum distension (NI) to luminal closure (see plot lower middle, note impedance presented relative to baseline and reversed in direction). Variables DCL, DPE and RP were combined to derive the pressure flow index (PFI) composite score.

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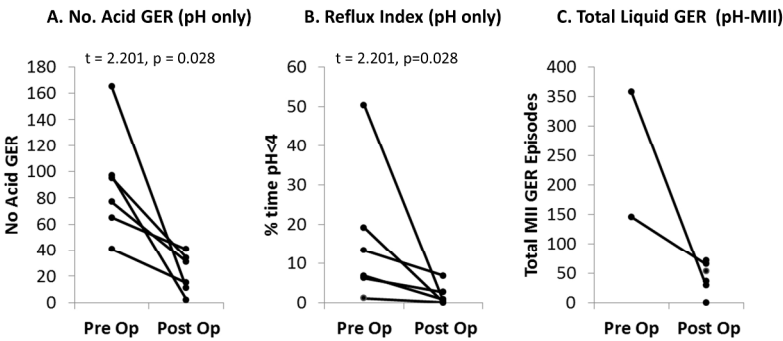
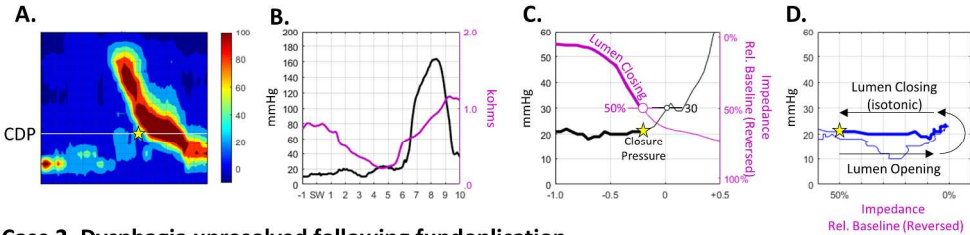


Figure 2. Reflux monitoring findings in six patients investigated by pH or pH-MII probe pre- and post-operatively due to symptom recurrence. Wilcoxon Signed Rank Test standardized t and p-value shown. Total liquid GER data (in C) are incomplete for four patients due to pH-MII not being performed pre-operatively.

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Case 1. Dysphagia resolved following fundoplication



Case 2. Dysphagia unresolved following fundoplication

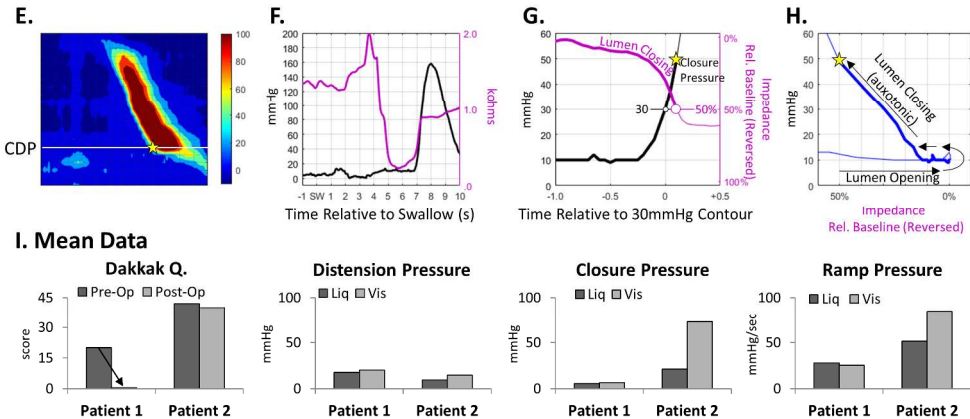


Figure 3. Pre-operative recordings and pressure-flow data from example Cases: Case 1 with pre-operative dysphagia that resolved post-operatively and Case 2 with significant persisting dysphagia. Tracings are based on recordings of 5ml viscous bolus swallows. Panels A and E show esophageal pressure topography of the distal esophagus with axial location of contractile deceleration point (CDP) marked. Panels B and F show pressure (black) and impedance (purple) profiles over time at the level of the CDP. Panels C and G show the pressure (black) and the impedance relative to baseline (purple) for the period 1 s before to 0.5s after the 30mmHg iso-contour (the direction of impedance change is reversed compared to B and F; 100% is pre-swallow baseline, 0% is maximum distension and 50% defines luminal closure). Note that the impedance-defined luminal closure (50%) occurs relatively later in time for Case 2, resulting greater clearance pressures being generated as the lumen closes. Panels D and H show the relationship between relative impedance (x axis) and pressure (y axis) over time. As seen in D, from Case 1, the lumen opens and then closes without any change in clearance pressure (known as isotonic contraction). As seen in H, from Case 2, the lumen opens and then closes with clearance pressures increasing (known as auxotonic contraction). I shows bar charts of patient Dakkak scores and the average data for the relevant pressure-flow metrics derived for liquid and viscous bolus swallows. Note, markedly higher clearance pressures (RP and CP) for Case 2.

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