



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

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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 360o 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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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.

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Key Summary

1. The established knowledge on this subject

- 2 The ability to accurately predict post-operative dysphagia risk is of interest to
3 gastroenterologists. 'Pressure-flow' anomalies may be predictors of dysphagia symptoms
4 following anti-reflux surgery.
- 5 Past studies were performed using 'low-resolution' perfusion lower esophageal sphincter
6 sleeve-manometry.

7 2. What are the significant and/or new findings of this study?

- 8 Dysphagia symptoms were common in our pediatric GER disease patients who were
9 receiving diagnostic work up for anti-reflux surgery.
- 10 Of all parameters evaluated, bolus 'clearing pressures' were most reliably associated with
11 dysphagia symptoms.

1 2 Abstract 3

4 *Background:* The role of high resolution esophageal impedance manometry (HRIM) for
5 establishing risk for dysphagia after anti-reflux surgery is unclear. We conducted a prospective
6 study of children with primary GER disease, for whom symptoms of dysphagia to solids were
7 determined pre- and post-operatively and we examined for features that may predict post-operative
8 dysphagia.
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11 *Methods:* Thirteen children (aged 6.8 – 15.5 years) undergoing work up prior to 360° Nissen
12 fundoplication were included. A dysphagia score assessed symptoms. A HRIM procedure recorded
13 5ml liquid, 5ml viscous and 2cm solid boluses. We assessed esophageal motility, esophago-gastric
14 junction (EGJ) morphology, EGJ contractility and pressure-flow variables indicative of bolus
15 distension pressures and bolus clearance pressures. A composite pressure-flow-index score was also
16 derived.
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19 *Results:* Pre-operative pressure-flow index was positively correlated with post-operative dysphagia
20 score (viscous bolus $r = 0.771$, $p < 0.005$). Of three variables that comprise the pressure-flow index,
21 the ramp pressure measured during bolus clearance was the main driver of the effect seen (viscous
22 bolus $r = 0.819$, $p < 0.005$).
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25 *Conclusions:* In order to mitigate symptoms in relation to anti-reflux surgery, dysphagia symptoms
26 and esophageal function need to be pre-operatively assessed. In patients with normal motility, an
27 elevated clearance pressure (indicating a pressure increase during luminal closure), may predict
28 post-operative dysphagia.
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31 *Key Words:* gastroesophageal reflux; fundoplication; dysphagia; diagnosis
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1 2 **Introduction** 3 4

5 High resolution esophageal impedance manometry (HRIM) is now a widely available diagnostic
6 paradigm offering the ability to record esophageal pressure and bolus flow with high fidelity. New
7 objective biomechanical measures can be defined, which describe anatomical features, flow
8 resistance and muscle contractility. These new characterizations of esophageal function may
9 improve assessment, and may guide clinical decision making for esophageal motility disorders¹⁻³.
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12 The HRIM technique may play a role in the assessment children with primary gastroesophageal
13 reflux (GER) disease particularly for patients being considered for anti-reflux surgery⁴. By
14 capturing bolus swallows pre-operatively, HRIM can characterize the dominant esophageal motor
15 pattern and exclude a primary motor disorder, most importantly achalasia; which, while rare, may
16 cause symptoms of regurgitation, heartburn, chest pain in addition to dysphagia⁵⁻¹². HRIM may also
17 determine hypomotility^{3,9,10,13-16}, weak EGJ contractility^{9,16-24} and/or the anatomical separation of
18 the lower esophageal sphincter (LES) from the crural diaphragm consistent with hiatus hernia
19 subtype morphology^{3,20,25}. All of these features may be present in patients with primary GER
20 disease.
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23 The use of pre-operative HRIM assessments for establishing 'risk' for post-operative dysphagia has
24 posed a significant challenge and its role is currently unclear. In pediatric series, post-operative
25 dysphagia ranges from 12% - 40%^{26,27}. In some cases, dysphagia is intractable, with significant
26 impact on quality of life. Dysphagia symptoms may mar a procedure that has been otherwise
27 successful for reducing GER and may lead to a cascade of re-investigation and intervention. A
28 reliable pre-operative test to identify patients with a high post-operative dysphagia risk is eagerly
29 anticipated by clinicians and patients alike. The ability to accurately predict dysphagia risk would
30 enable a more informed evaluation before proceeding to fundoplication, compared to other
31 treatment options. To date we have published two reports suggesting that esophageal 'pressure-
32 flow' anomalies, detectable during HRIM investigation, may be predictors of dysphagia
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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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8 Despite the encouraging results suggestive of predictors of dysphagia^{28,29}, these past studies were
9 performed using ‘low-resolution’ perfusion lower esophageal sphincter sleeve-manometry. This
10 methodology has dropped out of favor for routine use due to the advent of solid-state high
11 resolution manometry. We therefore conducted a new prospective case-series study of children with
12 primary GER disease undergoing fundoplication to examine for features that may predict post-
13 operative dysphagia. To do so, we employed current state-of-the art HRIM recording of pressure
14 and impedance patterns, performed *Chicago Classification* and derived pressure topography and
15 pressure-flow analytics to assess esophageal motor function. Symptoms of dysphagia to solids were
16 determined both pre-operatively and post-operatively, allowing at least six months for early
17 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

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

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

14 Esophageal Pressure Topography Plot (EPT) Analysis

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

23 EGJ Dysfunction and Morphology

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25 EGJ barrier function was manometrically assessed through calculation of the EGJ contractile index
26 (EGJ-CI) and assessment of EGJ-crural diaphragm (CD) separation consistent with hiatus hernia.
27 EGJ CI reflects the contractility of the EGJ over a period of three respiratory cycles. To determine
28 EGJ CI, the margins of the EGJ were enclosed in a DCI box of three consecutive respiratory cycle's
29 duration. The EGJ-CI (mmHg.cm) was determined as DCI value in mmHg.s.cm divided by the
30 duration in seconds^{22,24}. Presence of hiatus hernia was determined by a visible separation of the LES
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1 and CD pressure peaks at rest. EGJ morphology was defined as Type I (no LES-CD separation),
2 Type II (partial separation) or Type III (full separation)³.
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7 Esophageal Pressure-flow Analysis

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10 Automated analysis (Figure 1) was applied to each swallow using purpose built software
11 (*Esophageal AIMplot*, copyright T Omari) programmed in MatLab (The MathWorks Inc, Natick,
12 MA, USA). Data based on *AIMplot* software algorithms have been previously published^{28,32,34-40}.
13 However, for this work, the software underwent substantial revision to improve reliability, with
14 focus on variables that have demonstrated most relevance in these past studies.
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20 Following uploading of swallow data in comma separated values format (.csv), the analyst selected
21 five key temporal and anatomical landmarks from a pressure topography plot; i) swallow onset, ii)
22 esophageal proximal margin, iii) transition zone, iv) crural diaphragm and v) stomach. A separate
23 pressure topography plot was then generated, upon which superimposed lines showed the timing
24 and positions of the nadir impedance (indicating peak luminal distension) and the esophageal body
25 contractile peak. The user then fine-tuned the landmarks paying particular attention to the region
26 around contractile deceleration point (CDP) and the crural diaphragm position.
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39 Four classes of pressure-flow variable were then algorithmically derived; these are described below
40 and in Figure 1:
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44 1. *Intra-bolus distension pressure* during bolus transport was determined as the pressure at nadir
45 impedance. The average distension pressure (DP) was calculated for three anatomical regions
46 approximating the different phases of bolus transport. These were *DP during bolus accommodation*
47 (DPA, pressures UES to TZ), *DP during compartmentalized transport* (DPCT, pressures TZ to
48 CDP) and *DP during esophageal emptying* (DPE, pressures from CDP to CD; see Figure 1B).
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2 *2. Bolus clearance* was determined for the esophageal body from TZ to CDP based on the
3 *impedance ratio* (IR = nadir impedance divided by the impedance measured at the contractile peak).
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5 A higher IR indicates *less* effective bolus clearance (see Figure 1C)⁴¹.
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9 *3. Bolus flow latencies* were determined based on the pressure and impedance recording at the CDP
10 level. These were the *swallow to distension latency* (SDL) from swallow to nadir impedance and
11 *distension to contraction latency* (DCL) from nadir impedance to luminal clearance point. Luminal
12 clearance was defined by the 50% recovery of impedance relative to baseline (see Figure 1C) this
13 criterion for luminal clearance/closure has been previously validated and is in widespread use.^{42,43}
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17 *4. Pressures generation during bolus clearance (or clearance pressures)* were measured over time
18 from nadir impedance to luminal closure within the distal esophagus (25% of TZ to CDP length).
19 The *closure pressure* (CP) was defined as pressure measured at the time of luminal closure (50%
20 recovery of impedance relative to baseline) and the *ramp pressure* (RP) was determined by the
21 mean gradient of pressure change over time during closure (Figure 1C). Note RP has also been
22 called *IBP slope* in past publications^{28,29}.
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26 The *pressure-flow index* (PFI) is a composite score derived by combining distension pressure, ramp
27 pressure and flow latency variables using the following formula: $PFI = (DPE*RP)/DCL$
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30 Bolus Flow Time

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

1 2 Results 3 4

5 Patients 6 7

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

20 21 *Pre-Operative Clinical Findings* 22 23

24 The relevant clinical data for the 13 included patients are shown in Table 1. Most patients had a
25 reported clinical history of typical symptoms of heartburn and/or regurgitation. Eleven had one or
26 more abnormal finding on 24 hour pH-MII probe (abnormal reflux index, abnormal reflux
27 frequency and/or positive symptom association probability) and three showed endoscopic
28 esophagitis. None of the patients showed macroscopic signs of EoE, eosinophil counts in biopsy
29 specimens ranged 0-5 eos/hpf thus none met the established clinical definition of EoE (≥ 15
30 eos/hpf). Seven patients were radiologically investigated by barium swallow and all were reported
31 to have normal esophageal bolus transit. EGJ barrier dysfunction on HRIM was apparent in six of
32 the patients, of whom one had evidence of hiatus hernia (partial LES-CD separation consistent with
33

1 a Type 2 EGJ Morphology). Two patients had evidence of esophageal body contractile weakness
2 consistent with a CC V3.0 diagnosis of *ineffective esophageal motility* (IEM)³. Five patients were
3 on PPI therapy when followed up post-operatively (Table 1).
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9 [Table 1 here]
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15 *Pre-Operative Dysphagia Questionnaire*
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18 Pre-operative Dakkak dysphagia scores for all participants can be seen in Table 1, eight children
19 returned a pre-operative Dakkak score >10 indicative of pre-operative dysphagia to solids. During
20 liquid swallows, higher proximal distension pressure (DPA) and longer bolus flow time (BFT)
21 correlated with greater pre-operative Dakkak scores (Table 2). However, neither parameter was
22 significantly different based on grouped analyses comparing those patients with and without pre-
23 operative dysphagia. Pre-operative EGJ-CI did not correlate with pre-operative Dakkak scores ($r =$
24 0.463, ns), however was the only other parameter to be associated with pre-operative dysphagia on
25 grouped analysis being higher in patients reporting dysphagia (dysphagia 30.9 (15.1) mmHg.cm vs.
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27 no dysphagia 13.3 (11.9) mmHg.cm, $t = 2.201$, $p=0.050$).
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39 [Table 2 here]
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45 *Post-Operative Dysphagia Questionnaire*
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48 Five of the eight patients with pre-operative dysphagia improved post-operatively with
49 fundoplication surgery decreasing their Dakkak scores to <10 (Table 1). However, four patients
50 reported significant dysphagia post-operatively; three with persisting dysphagia and one with 'new'
51 dysphagia (14 year old boy with Dakkak 0 pre-operatively increasing to Dakkak 18 post-
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60 operatively).

1 Six patients were investigated by 24 hour pH/pH-MII probe after the surgery on clinical grounds
2 due to symptom recurrence. This showed that the surgery was highly effective in reducing
3 esophageal acid exposure, even though symptoms were refractory (Figure 2). These patients had
4 significantly greater dysphagia post-operatively than those without refractory symptoms (Dakkak
5 13[8, 23] in refractory patients vs. 0[0, 2.2] in other patients, $t = 3.095$, $p = 0.001$), suggesting that
6 post-operative dysphagia symptoms may have been a contributor underlying the post-operative
7 investigations.

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

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

32 Of the parameters measured pre-operatively, higher ramp pressure, closure pressure and pressure-
33 flow index were most significantly correlated with post-operative Dakkak score and, for all of these
34 variables, correlations based on viscous swallows were superior (Table 3). Grouped analysis based
35 on patients with and without post-operative dysphagia also showed that pre-operative viscous bolus
36 clearance pressures were higher in those who had post-operative dysphagia compared to those who
37 did not have post-operative dysphagia (RP 47 [27, 71] mmHg/s vs. 13 [10, 18] mmHg/s
38 respectively, $p = 0.002$ and CP 72 [48, 100] mmHg vs. 31 [25, 38] mmHg respectively, $p=0.002$).
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40 Consistent with the findings in relation to pre-operative dysphagia, BFT was longer pre-operatively
41 (Table 3) in patients with post-operative dysphagia compared to those without dysphagia (liquid
42 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
43 (0.27) sec respectively, $p = 0.025$). Pre-operative EGJ-CI did not correlate with post-operative
44 Dakkak scores ($r = 0.119$, ns).

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2 [Table 3 here]
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45 In order to help clarify and explain our main results in relation to post-operative dysphagia we
6 provide two case examples that are illustrative of these findings:
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10 Case 1: A child with pre-operative dysphagia that resolved (Figure 3 A-D)
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1213 A 9 year old female with symptoms of regurgitation and vomiting who had evidence of esophagitis
14 on endoscopy and a positive symptom association to heartburn symptoms on pH-MII study. Pre-
15 operative HRIM showed minor evidence of distal pressure compartmentalization, however
16 esophageal motility was considered normal (no hiatus hernia, EGJ-CI 43 mmHg.cm, mean liquid
17 DCI 1960 mmHg.cm.s and IRP4s 12 mmHg). The patient reported dysphagia to solids pre-
18 operatively (Dakkak 20) which resolved following fundoplication (Dakkak 0). The patient was
19 considered to be successfully treated without symptom recurrence.
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2122
23 Case 2: A child with pre-operative dysphagia that did not resolve (Figure 3 E H)
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2526 A 16 year old female with symptoms of regurgitation and vomiting who was endoscopy normal but
27 had abnormal esophageal acid exposure (reflux index 19.2%) and positive symptom association to
28 regurgitation symptoms on 24 hour pH-MII study. Pre-operative HRIM showed no evidence of
29 distal pressure compartmentalization and esophageal motility was considered normal (No hiatus
30 hernia, EGJ-CI 32 mmHg.cm, mean liquid DCI 2541 mmHg.cm.s, IRP4s 10 mmHg). The patient
31 reported significant dysphagia pre-operatively (Dakkak 41.5) which *did not* resolve following
32 fundoplication (Dakkak 39.5). Repeat pH-MII probe demonstrated normalization of reflux
33 parameters.
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3536 When the pressure-flow analysis data derived for Case 1 and Case 2 were compared (Figure 3) there
37 were striking differences in relation to the clearance pressures (CP and RP) which were much
38 higher pre-operatively for the viscous swallows in Case 2 (Figure 3 I). In Case 2, luminal closure
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1 occurred much *later* in time (compare Panel B vs. Panel F in Figure 3) and a pattern of pressure
2 increase with diameter decrease, known as *auxotonic contraction*, was observed (Figure 3 H).
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7 *Effects of Surgery on Biomechanical Measures*
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10 Data were complete for liquid and viscous boluses only from the seven patients who agreed to
11 undergo repeat post-operative HRIM. The main effects of fundoplication surgery accounting for
12 bolus consistency were investigated by repeated measures ANOVA. Despite the small sample size a
13 number of anticipated trends were revealed (Table 4), most importantly an increase in distension
14 pressures in the distal esophagus and EGJ (higher DPE and IRP4) consistent with surgery
15 increasing esophageal emptying resistance. Other effects included lower proximal distension
16 pressures (DPA), suggesting improved proximal flow resistance, and a delay in the timing of
17 maximum bolus distension of the distal esophagus after swallows (longer SDL). The pressure-flow
18 index, which includes DPE in its calculation, was higher post-operatively. The esophageal clearance
19 pressures (RP and CP) which were strongly associated with post-operative dysphagia overall (Table
20 3), were not altered by surgery. EGJ CI, indicative of EGJ tone, was significantly increased by
21 surgery ($t = 5.595$, $p = 0.001$).
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38 [Table 4 here]
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1 Discussion

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5 Dysphagia symptoms and esophageal body function were investigated in children with GER disease
6 undergoing Nissen fundoplication surgery. The main findings of our study were; i) patients
7 frequently reported symptoms of dysphagia to solids pre-operatively, ii) fundoplication surgery
8 decreased dysphagia symptoms in most patients, however, one third of patients had post-operative
9 dysphagia and, iii) these patients, with refractory or new dysphagia were distinguishable pre-
10 operatively by the presence of elevated bolus clearing pressures.
11

12 When assessed pre-operatively, bolus hold up symptoms to solids were common and improved
13 following surgery. This suggests that primary GER disease was very likely to be a causal factor
14 underlying bolus hold up symptoms in most patients. The fact that few individual parameters
15 appeared to link to pre-operative dysphagia is consistent with the multifactorial nature of the
16 mechanisms that may underlie symptom generation in the pre-operative setting; i.e. before reflux as
17 an influencer of symptoms is mitigated. Our study also identified four patients in whom dysphagia
18 persisted or developed as a new symptom. In these patients, manometry-based evidence to further
19 corroborate primary GER disease diagnosis was absent; i.e. none of these patients had a low EGJ
20 CI, none with EGJ morphology consistent with hiatus hernia and none demonstrating an IEM
21 subtype. Our findings support a recent adult series showing EGJ-CI has clinical utility in assessing
22 EGJ barrier function at baseline and after surgery²².
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24 In the current study, the pre-operative clearing pressures, namely ramp pressure and closure
25 pressure, demonstrated the strongest correlations with post-operative dysphagia symptom scores.
26 This is not a new observation; associations of clearing pressures and bolus hold up perception have
27 been previously reported in the context of post-operative dysphagia^{28,29} and non-obstructive
28 dysphagia^{2,45-47} (note, in these previous studies clearing pressures were defined by the parameter
29 'IBP slope'). A consistent observation of the current and past studies was that the correlation of
30 greater symptoms with higher clearance pressures was most apparent when the heavier viscous and
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1 solid bolus consistencies were swallowed. Interestingly, in the subgroup of patients for whom pre-
2 and post-operative HRIM data was available, fundoplication increased EGJ resistance but had little
3 or no effect on clearance pressures. Bolus flow time, a parameter which is typically shorter in non-
4 obstructive dysphagia³⁷ and achalasia^{48,49}, was paradoxically *longer* in relation to dysphagia in our
5 study. Furthermore, the IRP4 parameter used to diagnose EGJ outflow obstruction was not
6 associated with dysphagia. These findings suggest that obstructed esophageal emptying is not a
7 causative factor for dysphagia within our study cohort. The most consistent data identifies higher
8 clearance pressures (RP and CP) as being a relevant feature. Furthermore, the phenomenon of high
9 clearance pressures appears to pre-exist surgery and, unlike known biomechanical markers of
10 esophageal emptying resistance (i.e. DPE and IRP4) are not altered by surgery. The pressure-flow
11 index composite score, being calculated based on a formula which includes both distension
12 pressures (DPE) and clearance pressures (RP) was found to be increased by surgery and was also
13 higher in relation to post-operative dysphagia. We remain hopeful that the derivation of the PFI may
14 provide a useful clinical measure to distinguish pressure-flow abnormalities in the context of
15 findings of otherwise ‘normal’ peristalsis. The optimal PFI cutoff criteria suggested by this study
16 are provided in Table 5.

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38 [Table 5 here]
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41 In order to understand our observations we need to recognize that resistance to bolus flow during
42 bolus transport occurs on a continuum with normal un-impeded flow at one extreme and obstructed
43 flow at the other extreme. Obstructed luminal flow can be deduced by the presence of high
44 compartmentalized distension pressures (for example, in relation to focal strictures and EGJ outflow
45 obstruction). However, if bolus flow is *impeded* rather than obstructed, then distension pressures
46 may be less relevant. In relation to impeded flow, clearance pressures which quantify bolus
47 pressurization superior to the bolus midpoint (i.e. towards and at the bolus tail) are important
48 because they drive bolus movement. A high clearance pressure suggests that the contraction, rather
49 than being *isometric* (pressure rise occurs with a closed lumen after the bolus has passed) is instead
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1 *auxotonic* (pressure increases with a closing lumen as the bolus passes, see Figure 3 H)^{2,50,51}. The
2 recording of *auxotonic* pressure-flow phenomena demonstrates that the demands placed on the
3 esophageal muscles to do mechanical work (expend energy) during bolus clearance are greater. The
4 most likely factor leading to auxotonic pressures is that the bolus is, for one or more reasons, ‘more
5 reluctant’ to move along the esophageal lumen. Various factors that are both intrinsic and extrinsic
6 to the swallowed bolus material influence how easily transportable by peristalsis the bolus will be.
7 For example, the rheology (resistance to flow) of the swallowed material is important in this setting;
8 solids resist flow and are associated with the highest clearing pressures³⁶. Additionally, there are
9 other *superimposed* factors that are unrelated to bolus consistency but that may still be relevant.
10 These include, i) the size of luminal aperture, ii) the stiffness of the esophageal wall and iii) the
11 surface ‘tackiness’ of the mucosal lining due to the presence/absence of luminal secretions which
12 influence surface-interaction and lubrication.

13 The mechanism(s) by which the rate of pressure change during the clearance phase of the bolus
14 and/or the max pressure generated behind the bolus tail may directly lead to bolus perception are
15 unclear. We assume that the relevant sensory afferent mechanisms are largely insensitive to the
16 *isotonic* and *isometric* contractile states of the distal esophageal wall, as these are the most
17 commonly encountered in health⁵⁰. However, the active tension produced in relation to a prolonged
18 *auxotonic* contractile state may be different as generating sufficient additional wall tension to
19 produce a noxious stimulus. In other words, we should assume that a bolus being transported that
20 has been orally processed to be soft, moist and slippery (via saliva coating and mucosal secretions
21 lining the esophagus all the way down) should not be felt. Conversely, a bolus that is hard, dry and
22 resistive should be felt in order to generate alarm sensations that will alter eating behavior.

23 However, in certain pathophysiological situations, a usually soft, moist and slippery bolus may be
24 rendered less easy to transport. If so, this will lead to the bolus being felt because its transport is
25 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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28 The strength of our study lies in the highly detailed characterization of symptoms, reflux, motility
29 and pressure-flow phenomena in a series of patients enrolled in a single center. Our data broadly
30 support the findings of two previous pre-post fundoplication studies^{28,29}, however we acknowledge
31 the need for a larger prospective study that takes advantage of these refined measurement and
32 analysis methods. As data from patients younger than six years of age were not included we caution
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1 against generalizing of our findings to younger pediatric GER disease patients. There are inherent
2 challenges for generating the high quality data needed for the HRIM study to be meaningful for the
3 type of analysis applied. For results to be reliable, children need to be able to tolerate the procedure
4 and repeat-swallow viscous bolus consistencies on command. Investigations of infants and toddlers
5 are the most challenging and the utility of our approach to investigate them pre-operatively was not
6 tested.

7
8 In conclusion, our study demonstrates that both dysphagia symptoms and a finding of normal
9 esophageal motility are common in pediatric GER disease patients receiving diagnostic work up for
10 anti-reflux surgery. In order to avoid symptom recurrence and a potential cascade of re-
11 investigations and interventions, dysphagia symptoms need to be correctly attributed to GER
12 disease. In the absence of manometric evidence consistent with GER disease; such as IEM and a
13 hypotensive or disrupted EGJ, then pressure-flow analytics may detect subtle abnormalities that
14 may be symptom generating. Clearance pressures are quantifiable phenomena that may explain
15 dysphagia symptoms and predict post-operative symptom emergence or recurrence in the context of
16 otherwise normal esophageal motility. The underlying factors that may contribute to the finding of
17 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 = 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.

1
2 **Figure 2. Reflux monitoring findings in six patients investigated by pH or pH-MII probe pre-**
3 **and post-operatively due to symptom recurrence.**
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7 Wilcoxon Signed Rank Test standardized t and p-value shown. Total liquid GER data (in C) are
8 incomplete for four patients due to pH-MII not being performed pre-operatively.
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For Peer Review

Figure 3. Pre-operative recordings and pressure-flow date 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	
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	New or Persisting (Dakkak > 10)
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.

Pre-Op Metric	Metric vs. Pre-Op Dakkak Score		
	LIQ	VIS	Solid
Esophageal Pressure Topography			
	DCI	0.085	-0.028
	CFV	-0.094	-0.240
	DL	-0.247	-0.413
Intrabolus Distension Pressures	IRP4s	-0.342	-0.455
	DPA	0.554(0.05)	0.336
	DPCT	0.314	0.229
	DPE	-0.008	0.160
Intrabolus Clearance Pressures	RP	0.336	0.179
	CP	0.466	0.287
			-0.212
			-0.402
Flow/Distension Timing			
	SDL	0.074	-0.264
	DCL	-0.234	-0.163
			-0.259
Composite Measures			
	Pressure Flow Index	0.369	0.309
	Impedance Ratio	0.094	0.163
	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).

Pre-Op Metric	Metric vs. Post-Op Dakkak Score		
	LIQ	VIS	Solid
Esophageal Pressure Topography			
	DCI	0.402	0.445
	CFV	0.235	0.173
	DL	-0.270	-0.088
Intrabolus Distension Pressures	IRP4s	0.235	0.204
	DPA	-0.167	0.249
	DPCT	-0.040	-0.119
	DCE	-0.028	-0.062
Intrabolus Clearance Pressures	RP	0.230	0.819***
	CP	0.337	0.802***
Flow/Distension Timing	SDL	-0.261	-0.023
	DCL	0.014	-0.145
Composite Measures			
	Pressure Flow Index	0.366	0.771***
	Impedance Ratio	-0.184	-0.028
	Bolus Flow Time	0.584*	0.527(0.064)
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).			

Metric	Time Point		Main Effects RM-ANOVA	
	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
Intrabolus Distension Pressures	IRP4s mmHg 9.0 (5.9, 12.1)	13.5 (7.7, 19.3)	↑F 4.811, p 0.071	-
	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				
	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.

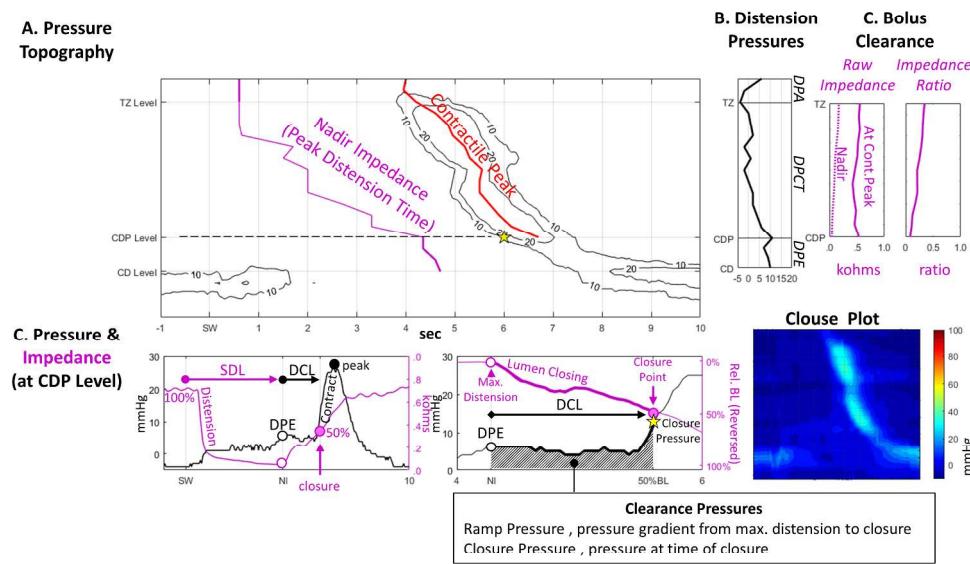


Figure 1. Derivation of Pressure-Flow metrics. Automated analysis was applied to each swallow within a region of interested (see inset Clouse plot lower right). A. A pressure topography iso-contour plot with superimposed lines showing the position of the nadir impedance (thick purple line; indicating 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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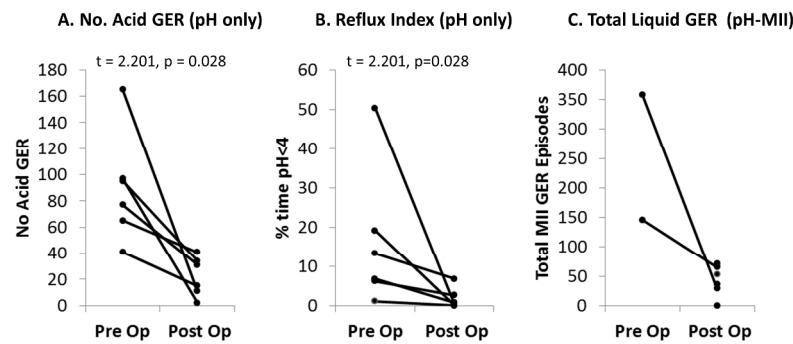


Figure 2. Reflux monitoring findings in six patients investigated by pH or pH-MII probe pre- and post-operatively due to symptom recurrence.

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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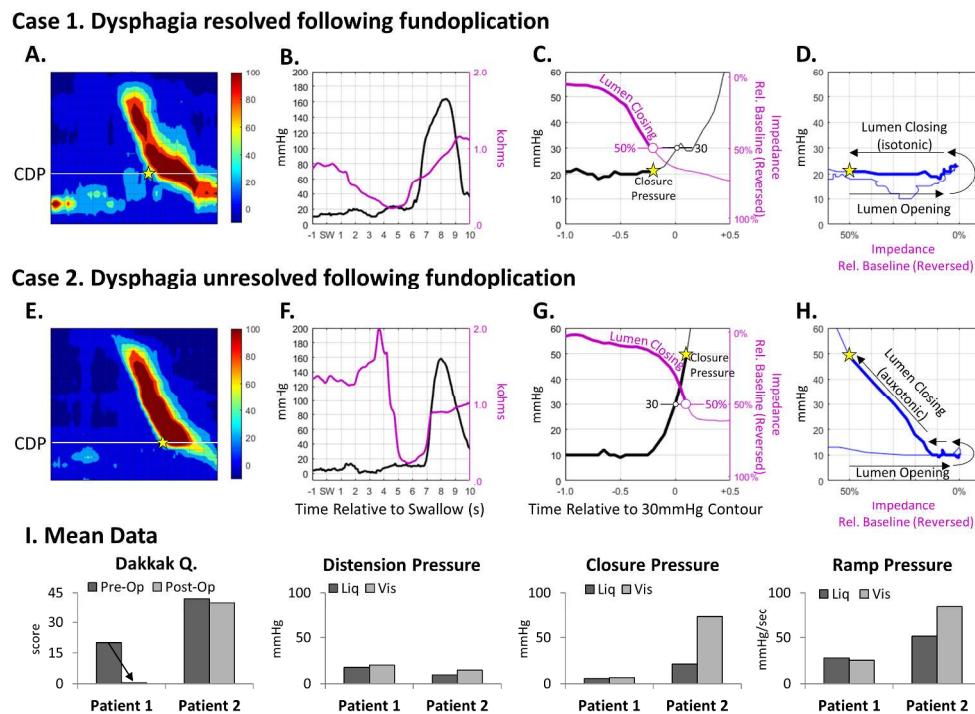


Figure 3. Pre-operative recordings and pressure-flow data from example Cases: Case 1 with pre-operative dysphagia that resolved post-operatively and Case 2 with significant persisting dysphagia. Tracings are based on recordings of 5ml viscous bolus swallows. Panels A and E show esophageal pressure topography 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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