High-resolution esophageal manometry in pediatrics: Effect of esophageal length on diagnostic measures

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Abstract

Background: High-resolution esophageal manometry (HREM), derived esophageal pressure topography metrics (EPT), integrated relaxation pressure (IRP), and distal latency (DL) are influenced by age and size. Combined pressure and intraluminal impedance also allow derivation of metrics that define distension pressure and bolus flow timing. We prospectively investigated the effects of esophageal length on these metrics to determine whether adjustment strategies are required for children.

Methods: Fifty-five children (12.3 ± 4.5 years) referred for HREM, and 30 healthy adult volunteers (46.9 ± 3.8 years) were included. Studies were performed using the MMS system and a standardized protocol including 10 × 5 mL thin liquid bolus swallows (SBM kit, Trisco Foods) and analyzed via Swallow Gateway (www.swallowgateway.com). Esophageal distension pressures and swallow latencies were determined in addition to EGJ resting pressure and standard EPT metrics. Effects of esophageal length were examined using partial correlation, correcting for age. Adult-derived upper limits were adjusted for length using the slopes of the identified linear equations.

Key Results: Mean esophageal length in children was 16.8 ± 2.8 cm and correlated significantly with age (r = 0.787, P = .000). Shorter length correlated with higher EGJ resting pressure and 4-s integrated relaxation pressures (IRP), distension pressures, and shorter contraction latencies. Ten patients had an IRP above the adult upper limit. Adjustment for esophageal length reduced the number of patients with elevated IRP to three.
Conclusions & Inferences: We prospectively confirmed that certain EPT metrics, as well as potential useful adjunct pressure-impedance measures such as distension pressure, are substantially influenced by esophageal length and require adjusted diagnostic thresholds specifically for children.

KEYWORDS
adjustment, Chicago classification, children, high-resolution esophageal manometry, impedance

1 | INTRODUCTION

Upper gastrointestinal symptoms, such as regurgitation, chest pain, and dysphagia are common in children and esophageal motility disorders and are often considered in the differential diagnosis. High-resolution esophageal manometry (HREM) with esophageal pressure topography (EPT) has standardized the assessment of esophageal motility. The Chicago Classification (CC) framework provides a diagnostic classification of esophagogastric junction (EGJ) outflow disorders including achalasia, and major and minor disorders of peristalsis. EPT criteria have not been developed for the pediatric population; therefore, implementation of the CC for the analysis of pediatric HREM studies has been challenging. Recent retrospective pediatric studies have identified age- and size-related differences with smaller/younger children demonstrating higher integrated relaxation pressure (IRP 4s), higher distal contractile integral (DCI), and shorter distal latency (DL). These effects appear to relate to esophageal organ growth, rather than developmental changes in neurological pathways and mechanisms.

The probability of an incorrect EPT diagnosis of a major motility disorder, such as disorders of EGJ outflow and/or esophageal spasm, increases if no age-appropriate normal values are used. When applied with impedance, HREM is able to quantify other critical biomechanical factors that may lead to symptom generation, most importantly failure of complete bolus transport and elevated luminal distension pressures. Enhanced pressure-impedance-derived metrics potentially identify causes of dysphagia and allow determination of biomechanical changes associated with procedures such as Nissen fundoplication, laparoscopic gastric banding, and EGJ dilatation. These novel methods were recently generalized via the web-based application Swallow Gateway™. However, the effect of esophageal length on integrated pressure-impedance metrics has not been evaluated and, while previously described, the effect on standard EPT metrics requires confirmation and quantification for clinical use. We therefore undertook a prospective study to investigate which of the suite of diagnostic parameters currently calculable by Swallow Gateway™ are influenced by shorter esophageal length and, for those parameters affected, to develop adjustment strategies to enable HREM analysis to be correctly applied.

Key Points
• In children, patient’s size influences high-resolution esophageal manometry (HREM) derived esophageal pressure topography (EPT) metrics. The influence of patient’s size on HREM derived combined pressure and intraluminal impedance metrics is unknown. We prospectively investigated the effects of esophageal length on these HREM metrics to determine whether adjustment strategies are required for children.
• Based on HREM data of 50 children referred for clinical investigation, we found shorter esophageal length to correlate with higher esophagogastric junction resting pressure, 4-s integrated relaxation (IRP), distension pressures, and shorter contraction latencies.
• Our study confirms previously described effects of esophageal length on EPT metrics that are used in the Chicago Classification of esophageal motility disorders and adds to this information by describing effects on measures of bolus distension pressure and flow timing.

2 | METHODS

2.1 | Patients

Data from pediatric patients (age 0-18 years) referred for clinical HREM at the Gastroenterology Unit of the Women’s and Children’s Hospital, Adelaide, Australia, between March 2018 and March 2019 were prospectively captured (de-identified) as part of an ongoing pediatric motility service clinical audit of routine assessment, and no informed consent from patients was required.

2.2 | Controls

Patients were compared to a cohort of 30 healthy adult volunteers (11 male, mean age 46.9 ± 18.5 [19-78] years, BMI 23.3 ± 3.8 [17.4-31.5] kg/m², mean esophageal length 20.0 ± 1.5 [range 16.8-22.6] cm) who were prospectively recruited via community advertisement. Adult control participants gave informed consent. Subjects reported no
signs and symptoms of dysphagia or gastroesophageal reflux disease; did not have a history of diabetes; oropharyngeal, cervical, or upper gastrointestinal surgery; allergy to local anesthetic and were not taking any medications known to alter gut motility. Based on standard EPT analysis and established diagnostic thresholds, most controls had normal motility according to the CC V3.0 (n = 27, 90%), the remaining three controls had ineffective esophageal motility (IEM).

### 2.3 HREM protocol

Motility recordings in patients and controls were performed according to the same protocol and with a 2.5-mm-diameter solid-state catheter incorporating 32 1-cm-spaced pressure sensors and 16 2-cm-long impedance segments (Unisensor USA Inc, Portsmouth, NH). Topical anesthesia (2% lignocaine spray or gel) is used if required (case by case), and patients are studied sitting in a semi-reclined posture. Clinical pediatric HREM in our Center is typically performed off proton-pump inhibitors (minimum 72 hours). Raw data were acquired at 20 Hz (Solar GI acquisition system, MMS, The Netherlands). The bolus test protocol optimally includes repeat administration (at >20-seconds intervals) of 10 × 5mL thin liquid and 10 × 5 mL extremely thick liquid. In addition, 10 × 1 cm² solid (white bread) may be trialed (case by case). While the protocol is usually well tolerated the number of repeats may be titrated down (case by case). The minimum

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**FIGURE 1** Derivation of swallow function metrics. The central plot shows esophageal pressure topography during swallowing of a 5 mL thin liquid bolus. Pressures generated along the esophagus and the esophagogastric junction (EGJ) are shown by colors (reds show highest pressure), and distension by the swallowed bolus is determined using impedance (pink line indicating peak distension). The plots above and below show the pressure and impedance signals at the upper esophageal sphincter (UES) and EGJ region margins which record bolus distension as liquid is transported from esophagus into stomach. The plot right shows the axial pressures recorded along the esophageal body at the time point when the lumen proximal of the EGJ was maximally distended (star symbol). The standard pressure topography metrics evaluated are shown in black or white text. These were (i) distal contractile latency time (DL), (ii) distal contractile integral (DCI, within yellow box), and (iii) 4s EGJ-integrated relaxation pressure (IRP 4s, within red box). The enhanced pressure-impedance-derived metrics are shown in pink text. Distension pressure (DP) measurements were guided by impedance. Three DP metrics (DPA, DPCT, and DPE) were determined to approximate the pressures during different phases of esophageal bolus transport; (iv) accommodation (DPA within region from UES (line a) to transition zone (TZ, line b), ie, a-b), (v) compartmentalized transport (DPCT from TZ to EGJ margin, ie, b-c), and (vi) esophageal emptying (DPE from EGJ margin to crural diaphragm (CD), ie, c-d). The other parameters evaluated included; (vii) the swallow to distension latency (SDL) and (viii) distension to contraction latency (DCL) which were both determined relative to when the lumen proximal of the EGJ was maximally distended (star symbol), (ix) impedance ratio (IR), a parameter defining bolus clearance, determined by the average of all ratio values along the esophageal body from UES to EGJ (see plot far right), and (x) pressure flow index (PFI), a composite score determined based on values for DPE, RP, and DCL (formula inset). PFI defines flow resistance at the EGJ.
pediatric protocol for a diagnostic outcome was completion of 2 × 5 mL thin liquid consistency swallows. To ensure standardized bolus conductivity across different consistencies, a commercially available bolus medium product conforming to the International Dysphagia Diet Standardization Initiative (IDDSI) was used (SBMkit, Trisco Foods Pty Ltd, Brisbane, Australia). Provocative multiple rapid swallow testing is sometimes utilized (case by case), and patients with a clinical suspicion of rumination spectrum disorder are given a light sandwich meal and then undergo a period of extended monitoring for up to 1 hour after commencement of study.13,16

2.4 HREM analysis
Pressure and impedance data were exported (asci format) and uploaded (de-identified) to the online Swallow Gateway™ application (open-access via www.swallowgateway.com) for analysis (Figure 1). The methodology for analysis of bolus swallows to derive swallow function metrics has been described in detail before.9,12-15,17-22 In cases of piecemeal repeat swallowing, the penultimate swallow was used to set swallow onset and calculate swallow latency. As the primary aim of this study was to assess esophageal length effects on physiological measures, studies with a minimum of two adequately captured liquid swallows were included, recognizing that we consider this number of swallows inadequate for accurate CC diagnosis. Resting EGJ pressure relative to gastric pressure was determined by derivation of the EGJ Contractile Index (EGJ-CI) over three respiratory cycles.23,24 Esophageal length (cm) was determined from the EPT plot by subtracting the position of UES lower margin from the position of the EGJ upper margin.

2.5 Statistical analysis
Statistical analysis was performed using SPSS Statistics 25 (IBM Corporation). Continuous data were summarized as mean ± SD or median (IQR) according to normality. Between-group comparisons (between patients with vs without history of gastrointestinal tract surgery and between patients vs controls) were performed using paired samples Student’s t test or Mann-Whitney U test. A P-value <.05 was considered to represent statistical significance. Partial correlations were performed to assess the relationship between esophageal lengths and swallow function metrics, while controlling for age. Multiple linear regressions were used to examine the relationship between metrics with clinical variables. Estimated cutoff values were created by using the slope of the linear equation defining the trend to estimate the optimal cutoff value for each metric. The mean esophageal length of healthy control subjects (20.0 ± 1.5 cm) was used to determine the threshold below which esophageal length-adjusted cutoff values should apply.

The maximum and/or minimum value for healthy adult controls served as the reference values for the metrics evaluated. For EPT metrics, adult normal values previously published by Bogte et al 2013,25 based on the same acquisition system and catheter technology, were additionally explored as a comparator.

3 RESULTS

3.1 Study cohort
Fifty-five pediatric patients underwent HREM investigation during the allotted period, and 50 were suitable for inclusion based on the completeness and quality of the HREM study (21 male, mean age 12.3 years, range 1.0-17.7 years). Median esophageal length of patients was 17.3 cm (range 9.9-22.2) vs 22.2 cm (range 16.8-22.6) in controls (P < .00) which correlated significantly with age and height (r = 0.787 and r = 0.834, respectively, both P < .0001).

Median number of liquid swallows captured suitable for analysis was 10 (range 2-15). Piecemeal deglutition occurred in 6 patients (age range 1-7.5 years). Included patients were mostly referred with a history of typical reflux symptoms (retrosternal pain, nausea, and/or vomiting). Six pediatric patients had esophageal atresia, and seven underwent antireflux surgery prior to HREM analysis, of which two were esophageal atresia patients. Thirty-five patients underwent diagnostic pH-impedance (pH-MII) monitoring with 16 returning abnormal findings. Eighteen patients were investigated with an extended postprandial protocol due to clinical suspicion of rumination spectrum disorder, and this confirmed the evidence of rumination in eight of the patients. Characteristics of patients and controls are shown in Table 1 and their outcomes of pH-MII and (extended) HRIM studies in relationship to Chicago Classification in Table 2.

3.2 Effect of esophageal length on diagnostic EPT metrics and Chicago Classification
Partial correlation was performed to determine the relationship between esophageal length and EPT metrics while controlling for age. DCI was significantly lower in patients with esophageal atresia compared to patients postfundoplication and patients without history of surgery of the GI tract (P < .001). Esophageal length was not correlated with DCI (r = 0.135, P = .263). None of the other EPT metrics differed significantly between the three patient groups. However, shorter esophageal length was correlated with higher EGJ-CI (r = −0.232, P = .041), higher IRP 4s (r = −0.434, P = .000), and shorter DL (r = 0.350, P = .003; Figure 2). Exclusion of patients with a history of gastrointestinal tract surgery was not on influence on the observed trends. Median IRP 4s and DL were also significantly higher and shorter, respectively, in children when compared to the healthy adult controls (13.7 mm Hg [IQR 9.4-13.7] vs 6.6 mm Hg [IQR 3.9-11.3]) and 6.7 seconds [IQR 6.0-7.1] vs 7.8 seconds [IQR 7.0-8.8], both P = .000.

Following adjustment for esophageal length, 10 patients were found to have an IRP 4s exceeding the upper limit set based on Swallow Gateway-derived adult values, of which one patient was post-esophageal atresia repair and one postfundoplication (Figure 2). One patient had had a known history of achalasia with recurring symptoms of dysphagia (patient 1). Despite having a borderline IRP 4s, one other patient showed a HREM pattern typical for achalasia.
correlation was performed to determine the relationship between esophageal length and enhance pressure-impedance metrics while controlling for the two included groups. Esophageal length was not correlated with ramp pressure (r = −0.078, P = .518), impedance ratio (r = −0.065, P = .592), or pressure flow index (−0.127, P = .151). However, shorter esophageal length was correlated with higher distension pressures throughout the esophageal body (Figure 3) and shorter swallow-distension latency (SDL; r = 0.550, P = .000) and distension to contraction latency (DCL; r = −0.270, P = .023). Exclusion of patients with a history of gastrointestinal tract surgery was not an influence on the observed trends. Of the three distension pressures evaluated, median DPE was significantly higher in children when compared to the healthy adult controls (7.0 mm Hg [IQR 3.2-11.6] vs 5.0 mm Hg [IQR 1.7-6.9], P = .017). SDL and DCL were also significantly shorter in pediatric patients vs adult controls (SDL = 3.1 seconds [IQR 2.4-3.6] vs 4.9 seconds [IQR 4.0-5.5], P = .000 and DCL = 3.5 seconds [IQR 2.9-4.5] vs 3.2 seconds [IQR 2.4-3.6], P = .026).

DPE, a potential adjunct measure supportive of EGJOO, was significantly higher in those patients with elevated IRP 4s value when compared to those with normal IRP 4s (10.7 mm Hg [IQR 7.9-17.2] vs 6.7 mm Hg [IQR 3.1-11.1], P = .016). Six patients showed elevated DPE above the adult cutoff. Four of these patients had borderline to elevated IRP 4s thus elevated DPE potentially supported an EGJOO diagnosis in these cases. However, two patients (6 and 7, Figure 3) with elevated DPE had normal IRP 4s suggesting adequate EGJ relaxation despite elevated DPE. In both cases, closer examination revealed that the period of elevated distension pressure was transient in association delayed timing of EGJ relaxation. The patients in question demonstrated complete esophageal bolus clearance based on the impedance recording and did not report solid bolus hold up (Dakkak score 0). Thus, while detectible, the clinical relevance of this pattern of elevated DPE in isolation remains unclear.

4 | DISCUSSION

This prospective study in children referred for HREM investigation confirms previously described effects of esophageal length on EPT metrics that are used in the Chicago Classification of esophageal motility disorders and adds to this information by describing effects on measures of bolus distension pressure and flow timing. Our study confirms that established diagnostic thresholds for some metric classes need to be adjusted for esophageal length. Consistent with our previous pediatric observations, IRP 4s increases and DL reduces in relation to shorter esophageal length. Esophageal length and associated luminal caliber vary from person to person, across age, gender, and ethnicity groups. Any effect of esophageal length must also be considered in association with a range of other physiological and pathological factors, including the passive wall properties, active neuro-mechanical properties, extrinsic compression imposed by other organs, the degree of

| TABLE 1 | Characteristics of pediatric patients and healthy adult controls |
|----------|---------------------------------------------------------------|
|          | Patients (n = 50)                                             | Controls (n = 30) |
|          | Age, y                                                        |                   |
|          | 12.3 ± 4.5 (1-18)                                            | 46.9 ± 3.8 (19-78) |
|          | Male gender (%)                                              |                   |
|          | 21 (42)                                                      | 11 (37)           |
|          | Weight, kg                                                   |                   |
|          | 49.9 ± 20.6 (9.0-102.0)                                      | 72.2 ± 12.8 (55.0-96.0) |
|          | Height, cm                                                   |                   |
|          | 159.9 ± 23.1 (82.0-193.2)                                    | 172.1 ± 7.9 (152.0-193.0) |
|          | Mean esophageal length, cm                                   |                   |
|          | 16.8 ± 2.8                                                   | 20.0 ± 1.5        |
|          | Median esophageal length, cm (range)                         |                   |
|          | 17.3 (9.9-22.2)                                              | 20.2 (16.8-22.6)  |
|          | BMI, z-score                                                 |                   |
|          | 20.0 ± 4.5 (11.9-30.6)                                       | 23.3 ± 3.8 (17.4-31.5) |
| Presenting symptoms n (%)a |                              |                   |
| Regurgitation/vomiting | 25 (50) | NA           |
| Dysphagia | 6 (12) |              |
| Chest pain | 8 (16) |              |
| Feeding difficulties | 4 (8) |              |
| Nausea | 4 (8) |              |
| Throat clearing | 2 (4) |              |
| Dental erosions | 1 (2) |              |

Abbreviation: BMI, body mass index.

aMultiple symptoms per patient possible. Data are mean ± SD (range).

type II with panesophageal pressurization and was diagnosed as such also supported by the clinical image and corroborative evidence of aberrant timed barium swallow (patient 2). One patient with esophageal atresia and eosinophilic esophagitis (patient 3) demonstrated panesophageal pressurizations that resembled that typically seen in Type II achalasia; this suggests esophageal outflow obstruction, possibly associated with EoE. A second patient who had suffered cerebrovascular accident (patient 4), developed swallowing difficulties after being prescribed the benzodiazepine drug, Cllobazam, to control seizures. This patient was therefore investigated on this therapy due to suspicion that the dysphagia may have been drug-induced, manometry demonstrated an elevated IRP 4s, and premature distal contraction thus resembling the pattern typical for Type III achalasia. The remaining seven patients with elevated IRP 4s values were considered “putative EGJOO.” Two patients had an average DL below the adjusted study cutoff (Figure 2); one was patient 4 as described above, the other was diagnosed with IEM as all swallows with short DL were ineffective (average DCI 102 mm Hg.cm.s, patient 5).

3.3 | Effect of esophageal length on enhanced pressure-impedance metrics

Impedance ratio was significantly higher in patients post-esophageal atresia repair and patients with achalasia (P = .001). None of the other pressure-impedance metrics differed between groups. Partial
### Table 2: Outcomes of pH-MII and (extended) HRIM studies in relationship with Chicago Classification

|                           | No history of surgery | Postfundoplication | Esophageal Atresia (EA) | Total |
|---------------------------|-----------------------|--------------------|-------------------------|-------|
|                           | 38/50 (76%)           | 6/50 (12%)         | 6/50 (12%)              |       |
| **pH-MII**                |                       |                    |                         |       |
| Abnormal                  | 10/38 (26%)           | Abnormal           | Abnormal                |       |
| Normal                    | 16/38 (42%)           | Normal             | Normal                  |       |
| Not performed             | 12/38 (32%)           | Not performed      | Not performed           |       |
| **Rumination Protocol**   |                       |                    |                         |       |
| Abnormal                  | 2/10 (20%)            | Abnormal           | Abnormal                |       |
| Normal                    | 8/10 (80%)            | Normal             | Normal                  |       |
| Not performed             | 11/16 (69%)           | Not performed      | Not performed           |       |
| **Diagnosis**             |                       |                    |                         |       |
| Secondary ruminating      | 2/38 (5%)             | Primary ruminating | Secondary ruminating    |       |
| GERD                      | 8/38 (21%)            | NA                 | GERD                    |       |
| Primary ruminating        | 5/38 (13%)            | NA                 | NA                      |       |
| NA                        | 23/38 (61%)           | NA                 | NA                      |       |
| **Chicago Classification**|                       |                    |                         |       |
| Achalasia                 | 0                     | 0                  | 0                       | 0     |
| EGJOO                     | 0                     | 1                  | 5                       | 0     |
| Absent                    | 0                     | 0                  | 0                       | 2     |
| IEM                       | 0                     | 3                  | 5                       | 1     |
| Normal                    | 2 (100%)              | 4 (50%)            | 3 (60%)                 | 1 (100%)|
|                           |                       |                    |                         |       |

**Note:** GERD defined as abnormal pH-impedance results (i.e., DeMeester score greater than 14.72 and pH less than 4.0 more than 5% of the total time) and clinical presentation with GER symptoms. Abbreviations: EA, esophageal atresia; EGJOO, esophageal gastric junction outflow obstruction; GERD, gastroesophageal reflux disease; HRIM, high-resolution impedance manometry; IEM, ineffective motility; NA, not applicable; pH-MII, pH-impedance.

*Patient 2 with borderline IRP of 22 mm Hg diagnosed with achalasia based on corroboratory evidence.

*Patient 3 with esophageal atresia and eosinophilic esophagitis and IRP 4s 26.7 mm Hg with panesophageal pressurization, fitting with an achalasia Type II-like pattern.

*Patient 4 with IRP 4s 27.3 mm Hg and mean DL 4.6 s, fitting with an achalasia Type III-like pattern, which was thought to be therapy-induced (Clobazam; See Figure 2).
FIGURE 2  Scatter-plots of A, mean IRP 4s and B, DL values for all subjects. Established adult cutoff criteria were considered applicable to those subjects with an esophageal length >20 cm (mean esophageal length of adult controls). Adjusted cutoff values were created by applying the linear equation defining the trends for esophageal length (solid gray line) at the limit of current adult controls (dashed green lines) and the cutoff based on Bogte et al 201325 (dashed orange lines). Gray dots: healthy adult controls; (black dots: pediatric patients. A, Upper limit for IRP 4s in healthy controls was 22.4 mm Hg. The following patients with elevated or borderline IRP 4s values are highlighted in red: Patient 1 is a 14-year-old female with known history achalasia (Type I) referred for worsening of dysphagia. Mean IRP 4s 30 mm Hg and absent peristalsis, consistent with a diagnosis of Type I achalasia. Patient 2 is a 13-year-old girl who was referred for longstanding solid dysphagia. HREM showed an IRP 4s 22 mm Hg and panesophageal pressurization. Despite the borderline IRP 4s, this patient was diagnosed with achalasia Type II based on corroborative evidence (barium swallow) and typical symptom presentation. Patient 3 is a 6-year-old male with a complex history of esophageal atresia, VACTERL association and eosinophilic esophagitis referred due to choking episodes. HREM showed an IRP 4s 26.7 mm Hg and panesophageal pressurization, fitting with an achalasia Type II-like pattern. Patient 4 is a 14-year-old girl with cerebral palsy referred for dysphagia. HREM showed a Type III-like pattern (mean IRP 4s 27.3 mm Hg and mean DL 4.6s) which was thought to be induced by benzodiazepine therapy (Clobazam) to control seizures. The remaining seven patients with elevated IRP 4s values are highlighted in white and considered ‘putative EGJOO’. B, Upper limit for DL in healthy controls was 6.0 s. Patients with shortened mean DL are highlighted in red, including Patient 4 as described above. Patient 5 is a 15-year-old female with dysphagia. Mean DL 5.2 seconds and 100% of swallows with DCI <450 mm Hg.cm.s (but >100 mm Hg.cm.s), therefore not fulfilling the CC criteria for DES and diagnosed with IEM. Arrows are pointing at those patients with shortened mean DL if the adult threshold would have been applied. IRP 4s: integrated relaxation pressure; DL: distal latency; EGJOO, EGJ outflow obstruction; IEM, ineffective esophageal motility

passive longitudinal stretch, active shortening, and the presence/absence of hiatus hernia morphology.

EGJ-CI is a metric to quantify the contractility of the EGJ during normal respiration23 and has been proposed a superior measure to discriminate normal from abnormal EGJ barrier function.24 The increase in EGJ-CI in smaller patients is almost certainly due to augmented wall tension due to reducing luminal size around a catheter of standard dimensions. This property also influences IRP 4s. However, IRP 4s is a more complex metric, being influenced by both luminal distension and wall contact pressures, and thus is subject to the effects of relative bolus volume and EGJ opening diameter. Without adjustment, misdiagnosis of EGJOO and achalasia, both major motility disorders, is more likely. DL is also a critically important parameter that detects premature contractions, which distinguish Type III achalasia and defines distal esophageal spasm (DES).

In the current study, one patient exhibited a Type III-like motility pattern which we suspect may have been related to a benzodiazepine therapy.

The additional new findings of this study are that esophageal distension pressures were higher and SDL, a measure of bolus flow latency, was shorter in association with shorter esophageal length suggesting earlier arrival of the bolus in the distal esophagus. While the potential diagnostic relevance of SDL is still to be determined, the measurement of distension pressure may be important for detection of luminal obstruction which may occur because of focal esophageal body rings, webs and strictures, malignancy or failure of neural lower esophageal sphincter relaxation. These results suggest that diagnostic criteria for potentially useful adjunct measures, such as distension pressure, should also be adjusted for esophageal length. In the current study, evidence of elevated IRP 4s was in only one case associated with elevated distension pressure. Two patients with otherwise normal motility had elevated esophageal distension pressures. Closer examination revealed in both cases a pattern of early bolus pressurization due to delayed timing of EGJ relaxation rather than failure of relaxation per se (Figure 3). Distension pressures rise with a smaller luminal capacity or increased volume of swallows. Higher distension pressures in pediatric patients are therefore consistent with the bolus being, in relative terms, larger in the esophageal lumen of younger/smaller patients. A recent study in a comparable pediatric cohort using endoluminal functional lumen imaging probe (FLIP) found distensibility of the esophageal lumen to correlate significantly with age, weight, and height. Increasing
esophageal caliber in older/taller children is likely to be a major factor underlying this observation.\textsuperscript{27}

Goldani et al\textsuperscript{5} previously proposed adjustment of DCI for esophageal length in children for the interpretation of hypotensive contraction. However, consistent with our previous findings, we did not
find a relationship between lower DCI values and shorter esophageal length. DCI is a complex metric that quantifies the length, vigor, and persistence of postdeglutitive pressurization in the distal esophagus. Although length and duration of the DCI region increase with esophageal length, the measured pressure decreases due to a reduced relative catheter lumen size in a wider esophagus. It is likely that these factors negate an overall trend.

Piecemeal deglutition occurs normally when the swallow mechanism is challenged with a larger than optimal bolus volume to break up an orally administered bolus into smaller more manageable volumes. This impacts biomechanical swallow measures and should thus be recognized in HRIM analysis. Piecemeal deglutition of liquid boluses occurred in six of our cohort and was more frequent in the younger patients (age range 1-7.5 years). In these cases, the 2-3 piecemeal swallows typically occurred in rapid succession and the penultimate swallow was used to set swallow onset and determine swallow latencies as this propagates the esophageal contrac tile wave. Thus, assessment of distal latency is most meaningful if assessed against the last swallow in the sequence to reflect peristaltic timing. Piecemeal swallow is unavoidable in many cases, and therefore, we believe that exclusion on these grounds would exclude younger children from this dataset.

The strengths of our study include a prospective design and use of a HREM protocol based on a standardized volume and bolus medium (SBMkit). All studies in both patients and controls were carried out by using the same manometric catheter design. Esophageal length and swallow onset were reliably determined by visualization of the UES high pressure zone, and impedence indication of bolus flow. However, our study had limitations which are important to acknowledge. Firstly, due to ethical considerations, we included a heterogeneous cohort of pediatric patients referred for HREM, rather than asymptomatic pediatric controls (not ethically possible). The study population was predominantly comprised of gastroesophageal reflux disease patients, who typically displayed normal or minor esophageal motor disorders, and therefore were the most ideal patient population to include for a study of this nature. Some patients were postesophageal atresia repair, and some were postfundoplication; these patients were included as we hypothesized that their esophagus would achieve normal growth after surgery. Additional analyses revealed that their results did not lie outside the overall distribution and therefore did not skew the dataset. Additionally, as the clinical relevance of a diagnosis of IEM remains a matter of current debate, we did not exclude controls with IEM as they appear to have the same symptom profile and barium study findings as patients with normal motility according to the CC.

Our study was neither designed nor powered to explore more complex associations among HREM metrics, clinical symptoms (eg, dysphagia), and other tests (eg, pH-MII monitoring), and this remains a topic for further prospective research in larger more homogeneous datasets. The youngest patient able to tolerate the procedure and swallow 5 mL boluses was 1 year of age. Obtaining useful HREM data in the very young is challenging as it requires them to tolerate the procedure and repeat-swallow on command. Further studies are required to establish a standardized protocol and relevant criteria for patients <1 year.

In conclusion, we analyzed a prospective series of clinical HREM studies in a pediatric cohort to tailor criteria for diagnosis of esophageal motility disorders. We have prospectively confirmed that, in relation to 5 mL bolus swallows, certain EPT metrics are substantially influenced by age/size and that this can change the diagnosis based on the CC algorithm. The ability to reliably derive enhanced metrics, like distension pressure, has been generalized via the open-access, non-commercial web application Swallow Gateway™. These physiological measures, adjustable for patient esophageal length, may have adjunct value which complement a CC diagnosis, or detect pressurization phenomena that may explain symptoms. The current study suggests that analytical software could be upgraded with automated age adjustment of diagnostic thresholds specifically for pediatric patients. Further research is needed to determine normative thresholds to support pediatric use of the other manometric systems in current use.

CONFLICT OF INTEREST

T Omari has patent inventorship and copyrights over the analytical methods described. The open-access Swallow Gateway™ resource is provided and hosted by Flinders University. The other authors have no conflicts of interest relevant to this article to disclose.

AUTHOR CONTRIBUTIONS

MMJS and TIO designed the research study, performed the research, analyzed the data, and wrote the paper. TIO coordinated and supervised the study. DM, RC, PH, and RA included the patients. LM,
GS, and KL performed the HREM studies in patients; LF, TI, and CC recruited healthy controls and performed their HREM studies. CC, MB, and MW provided the manuscript with important intellectual content.

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INSTITUTIONAL REVIEW BOARD STATEMENT
Pediatric data for this study were collected under a Clinical Audit and approved by the Women’s and Children’s Hospital Human Research Ethics Committee (Protocol No.1062A approved October 2018). Adult control participants were recruited under Southern Adelaide Clinical Human Research Ethics Committee (Protocol No. 76.17 approved November 2017). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

INFORMED CONSENT
This study was conducted as a prospective clinical audit of routine assessment and no informed consent from patients was required. Adult control participants gave informed consent.

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REFERENCES
1. Kahrilas PJ, Bredenoord AJ, Fox M, et al. The Chicago classification of esophageal motility disorders, v3.0. Neurogastroenterol Motil. 2015;27(2):160-174.
2. Singendonk MM, Smits MJ, Heijting IE, et al. Inter- and intrarater reliability of the Chicago classification in pediatric high-resolution esophageal manometry recordings. Neurogastroenterol Motil. 2015;27(2):269-276.
3. Singendonk M, Rosen R, Oors J, et al. Intra- and interrater reliability of the Chicago Classification of achalasia subtypes in pediatric high-resolution esophageal manometry (HRM) recordings. Neurogastroenterol Motil. 2017;29(11):e13113.
4. Singendonk MM, Kritas S, Cock C, et al. Applying the Chicago classification criteria of esophageal motility to a pediatric cohort: effects of patient age and size. Neurogastroenterol Motil. 2014;26(9):1333-1341.
5. Goldani HA, Staiano A, Borrelli O, Thapar N, Lindley KJ. Pediatric esophageal high-resolution manometry: utility of a standardized protocol and size-adjusted pressure topography parameters. Am J Gastroenterol. 2010;105(2):460-467.
6. Omari TI, Szczesniak MM, Maclean J, et al. Correlation of esophageal pressure-flow analysis findings with bolus transit patterns on videofluoroscopy. Dis Esophagus. 2016;29(2):166-173.
7. Omari TI, Wauters L, Rommel N, Kritas S, Myers JC. Oesophageal pressure-flow metrics in relation to bolus volume, bolus consistency, and bolus perception. United European Gastroenterol J. 2013;1(4):249-258.
8. Rommel N, Van Oudenhove L, Tack J, Omari TI. Automated impedance manometry analysis as a method to assess esophageal function. Neurogastroenterol Motil. 2014;26(5):e636-e645.
9. Singendonk M, Kritas S, Omari T, et al. Upper gastrointestinal function in morbidly obese adolescents before and 6 months after gastric banding. Obes Surg. 2018;28(5):1277-1288.
10. Singendonk MM, Kritas S, Cock C, et al. Pressure-flow characteristics of normal and disordered esophageal motor patterns. J Pediatr. 2015;166(3):690-696.e691.
11. Singendonk M, Omari TI, Rommel N, et al. Novel pressure-impedance parameters for evaluating esophageal function in pediatric achalasia. J Pediatr Gastroenterol Nutr. 2018;66(1):37-42.
12. Singendonk M, Cock C, Bieckmann L, et al. Reliability of an online analysis platform for pharyngeal high-resolution impedance manometry recordings. Speech, Language and Hearing. 2018;1:9.
13. Singendonk M, Benninga MA, van Wijk MP, Abu-Assi R, Omari TI. Letter in response to Rosen et al.: an interesting pediatric case of rumination syndrome. Neurogastroenterol Motil. 2018;30(10):e13452.
14. Omari T. Addendum to a study of dysphagia symptoms and esophageal body function in children undergoing anti-reflux surgery. United European Gastroenterol J. 2018;6(8):1274-1275.
15. Omari T, Ferris L, Cajander P, et al. Tu1653 - a standardized test medium to detect bolus-related modulation of the pharyngeal swallow during high-resolution pharyngeal manometry. Gastroenterology. 2018;154(6):S-982-S-983.
16. Carlson DA, Roman S. Esophageal provocation tests: are they useful to improve diagnostic yield of high resolution manometry? Neurogastroenterol Motil. 2018;30(4):e13321.
17. Cock C, Omari T. Diagnosis of swallowing disorders: how we interpret pharyngeal manometry. Curr Gastroenterol Rep. 2017;19(3):11.
18. Ferris L, King S, McCall L, et al. Piecemeal deglutition and the implications for pressure impedance dysphagia assessment in pediatrics. J Pediatr Gastroenterol Nutr. 2018;67(6):713-719.
19. Omari TI, Dejaeger E, Tack J, Vanbeckevoort D, Rommel N. An impedance-manometry based method for non-radiological detection of pharyngeal postswallow residue. Neurogastroenterol Motil. 2012;24(7):e277-284.
20. Omari TI, Dejaeger E, van Beckevoort D, et al. A method to objectively assess swallow function in adults with suspected aspiration. Gastroenterology. 2011;140(5):1454-1463.
21. Omari TI, Rommel N, Szczesniak MM, et al. Assessment of intraluminal impedance for the detection of pharyngeal bolus flow during swallowing in healthy adults. Am J Physiol Gastrointest Liver Physiol. 2006;290(1):G183-188.
22. Schar M, Woods C, Ooi EH, et al. Pathophysiology of swallowing following oropharyngeal surgery for obstructive sleep apnea syndrome. Neurogastroenterol Motil. 2018;30(5):e13277.
23. Nicodeme F, Pippa-Muniz M, Khanna K, Kahrilas PJ, Pandolfino JE. Quantifying esophagogastric junction contractility with a novel HRM topographic metric, the EGJ-Contractile Integral: normative values and preliminary evaluation in PPI non-responders. Neurogastroenterol Motil. 2014;26(3):353-360.
24. Gyawali CP, Roman S, Bredenoord AJ, et al. Classification of esophageal motor findings in gastro-esophageal reflux disease: conclusions from an international consensus group. Neurogastroenterol Motil. 2017;29(12):e13104.
25. Bogte A, Bredenoord AJ, Oors J, Siersema PD, Smout AJ. Normal values for esophageal high-resolution manometry. Neurogastroenterol Motil. 2013;25(9):762-e579.
26. Quader F, Reddy C, Patel A, Gyawali CP. Elevated intrabolus pressure identifies obstructive processes when integrated relaxation pressure is normal on esophageal high-resolution manometry. Am J Physiol Gastrointest Liver Physiol. 2017;313(1):G73-G79.
27. Menard-Katcher C, Benitez AJ, Pan Z, et al. Influence of age and eosinophilic esophagitis on esophageal distensibility in a pediatric cohort. Am J Gastroenterol. 2017;112(9):1466-1473.
28. Moreau B, Kambites S, Levesque D. Esophageal length: esophageal manometry remains superior to mathematical equations. J Pediatr Gastroenterol Nutr. 2013;57(2):236-239.

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