PEDIATRICS

Pediatric Esophageal High-Resolution Manometry: Utility of a Standardized Protocol and Size-Adjusted Pressure Topography Parameters

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OBJECTIVES: **Esophageal high-resolution manometry (EHRM) has evolved rapidly from a research tool to a routine investigation in adult clinical practice. This study proposes and evaluates a standardized EHRM protocol for use in pediatric clinical practice.**

METHODS: **Thirty pediatric patients underwent unsedated EHRM. Indications for EHRM were dysphagia, feeding difficulty, or pre-fundoplication assessment. Two 20-channel customized water-perfused silicone catheters, with an outside diameter of 3.8 mm (MuiScientific, Ontario, CA), were used. The catheters had one distal gastric channel, five channels 0.5 cm apart for the e-sleeve, and 14 proximal channels either 1 cm (for children <5 years) or 2 cm apart (for children >5 years). Single wet swallows, multiple rapid swallows (MRS), and solid swallows were systematically studied.**

RESULTS: **The median age was 10 years (range 6 months–15 years). The esophageal motor findings were normal peristalsis (n=15), peristaltic dysfunction (n=12), achalasia (n=3), and spasm on consumption of solid food (n=2). The distal contractile integral adjusted for esophageal length (DCIa) of patients with peristaltic dysfunction was significantly lower than that of patients without peristaltic dysfunction (P<0.001). On MRS, aperistalsis with lack of esophagogastric junction (EGJ) relaxation was observed in patients with achalasia, and aperistalsis with complete EGJ relaxation was observed in patients with severe peristaltic dysfunction. On consumption of solid food, esophageal spasm associated with bolus impaction was observed in two patients.**

CONCLUSIONS: **This study provides objective information with regard to topography pressure parameters in esophageal motility disorders of childhood while using a standardized EHRM protocol. The new DCIa variable may be useful for the assessment of patients with peristaltic dysfunction.**

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INTRODUCTION

Esophageal high-resolution manometry (EHRM) has revolutionized the performance of clinical esophageal manometry by showing the manometric data set acquired from a series of closely spaced manometric sensors located between the pharynx and stomach as pressure contour plots (1–3).

Pseudo-three-dimensional "topographic plots" are graphical representations of three independent parameters collected from these sensors along the length of the esophagus during swallowing, namely, time, sensor position, and average pressure (4,5); in effect, these plots provide a functional anatomy of the esophagus. The development of micromanometric water-perfused assemblies (6,7) and more recently, solid-state catheters with up to 36 channels (1,8), followed by a sophisticated software technology, facilitated an improved analysis with a move from snapshot views toward true "spatiotemporal plots" (9). An electronic "e-sleeve" can be applied during data analysis to provide stable and reliable measurements of lower esophageal sphincter (LES) function similar to that acquired using a conventional sleeve sensor with additional information relating to length and movement of the lower esophageal high-pressure zone (10,11).

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EHRM has facilitated the routine measurement and analysis of physiological parameters not normally appreciated during a conventional manometric evaluation of the esophagus. An appreciation of the "transition zone", which represents the functional separation between the proximal segment of striated muscle and the distal segment of smooth muscle (12,13), and the demonstration of spatial separation between the components of the reflux barrier, the LES and diaphragmatic crura, both important to esophagogastric junction (EGJ) integrity, have further advanced clinical insight into swallowing and its disorders (14,15).

Recently, a new classification of esophageal motility by pressure topography characteristics in adults has been proposed (16). Among the new parameters used to describe esophageal motility, the distal contractile integral (DCI) that quantifies the length, vigor, and persistence of postdeglutitive pressurization in the distal segment of the esophageal body has been proposed as a numerical descriptor of the esophageal peristaltic wave. DCI cutoff values are well established for hypertensive peristalsis in adults (16); however, the function of lower limits is not clarified and this parameter has not been reported in pediatric patients in whom esophageal length influences the DCI value.

Although EHRM study protocols and normative data are well established in adults (9,16), pediatric data are sparse, with only two published studies of esophageal body motility in preterm infants (17) and older children (18). Given the limitations of manometry studies in the pediatric group in a clinical setting, mainly because of catheter size and tolerability, this study proposes and evaluates a standardized protocol for performance and analysis of EHRM in children by adapting some topography pressure parameters primarily developed for analysis in adults. It also proposes and validates a new variable, DCI adjusted for esophageal length (DCIa) in children with and without peristaltic dysfunction.

METHODS

EHRM was performed on 31 consecutive patients referred to the Neurogastroenterology and Motility Service at Great Ormond Street Hospital, London, United Kingdom, for esophageal manometry between January 2008 and August 2008. The study protocol had been developed over the preceding 3 months in the setting of a tertiary-care practice specializing in the clinical management of esophageal disease.

Of the 31 patients, 30 underwent EHRM (MMS software, Enschede, the Netherlands) without sedation. One 2-year-old patient who did not tolerate the study without sedation was excluded. Indications for EHRM were dysphagia, feeding difficulty, or pre-fundoplication assessment. Underlying diseases included achalasia without good response to previous treatment, previous repair of esophageal atresia, postresection of mediastinal tumor, anomalous intrathoracic artery, systemic autoimmune disease, and previous unsuccessful fundoplication.

EHRM technique

EHRM was performed after a fasting period appropriate for each subject's age. Two different sizes of 20-channel silicone-customized water-perfused catheters, with an outside diameter of 3.8 mm (MuiScientific, Ontario, CA), were used. The catheters had 1 distal channel for gastric recording, 5 channels 0.5 cm apart for e-sleeve, and 14 proximal channels either 1 cm apart (for children under 5 years of age) or 2 cm apart (for those older than 5 years).

Microlumina were perfused with a pneumohydraulic perfusion system (MMS software) at a water perfusion rate of 0.15 ml/min. Pressure data were acquired and shown using software especially designed for high-resolution manometry (HRM; MMS v 8.8–8.11), which displays isobaric contour plots on three-dimensional views that resemble topographic plots of geographical elevations (3,19).

The catheter was inserted transnasally until the most distal recording site was positioned in the stomach and the respiratory inversion point was within the five e-sleeve channels (20,21). Data acquisition was started after the catheter was correctly placed in such a manner so as to obtain data from the stomach, e-sleeve, esophageal body, upper esophageal sphincter, and pharynx. No further movement of the catheter was required.

An approximately 3-min period of recording was initially carried out to assess the basal LES pressure. Three types of swallows were systematically tested, taking into consideration the limitations of young age and clinical history of feeding difficulty. First, water boluses (0.5–5.0 ml, depending on subject age and underlying symptoms) were given by syringe at 20 s intervals until at least 10 wet swallows were obtained. Patients under 5 years of age had 2.0 ml water boluses, whereas patients over 5 years of age had 5.0 ml. Only two patients younger than 1 year of age had 0.5 ml water bolus because of oropharyngeal dysphagia. Second, to test the sequence of multiple rapid swallows (MRS) and to study the inhibition of LES, approximately 100 ml of water or any preferential liquid was offered by straw, and patients were asked to drink at once as fast as they could, taking less than 1 min to do so. MRS was performed only in patients without oropharyngeal dysphagia and who were able to drink using a straw. Third, solid swallows were checked by offering at least one slice of toast or other solid food when these were known to induce dysphagia in a subject. Patients were asked to chew and swallow subsequent amounts of toast 2×3 cm in size. Solid food was offered only to patients who normally consumed it.

HRM analysis

Data were analyzed using MMS software version v8.11. Swallowing was determined by pharyngeal contraction, followed by the opening movement of the upper esophageal sphincter previously described in adult subjects.

Tracings were first characterized by the presence or absence of impaired deglutitive EGJ relaxation by measuring the lowest mean residual pressure over a 3 s interval within the postdeglutitive period. EGJ basal pressure was measured for periods without swallowing.

Following EGJ relaxation, the dominant characteristics of the esophageal contraction after swallows were assessed. This analysis was facilitated by the generation of isobaric contour plots at a 30 mm Hg threshold pressure, given that this is the minimum pressure to associate with complete bolus transit (16,22). Pressurization front velocity (PFV), expressed in cm/s, was calculated by the slope between the distal temporal margin of the transition zone and the upper margin

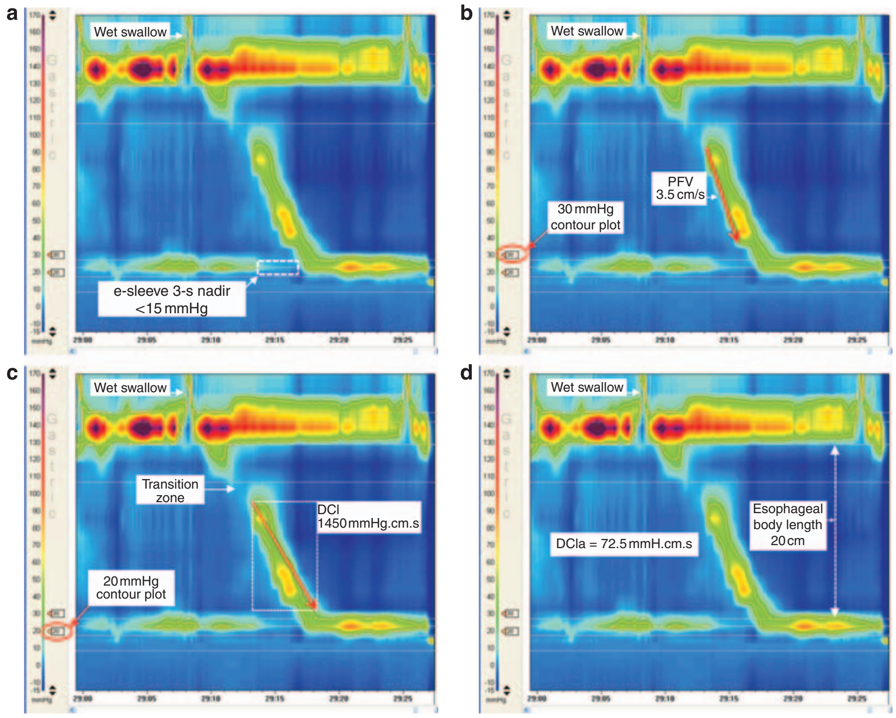

Figure 1. High-resolution manometry measurements. Esophagogastric junction (EGJ) relaxation was assessed using an automated measurement on MMS software of the lowest mean residual pressure over a 3-s interval within the postdeglutitive period (**a**). Derivation of pressurization front velocity (PFV) is the slope of the line linking the distal temporal margin of the transition zone with the proximal margin of the EGJ on the 30 mm Hg isobaric contour plot (**b**). The distal contractile integral (DCI) corresponds to the volume of the solid observed on the 3-D, spanning from the 20 mm Hg contour plot to its peak, expressed as mm Hg s cm. Measurements were determined by MMS software using the right click on the mouse (**c**). Esophageal body length considered as the linear distance between the upper esophageal sphincter lower limit and the LES upper limit was used to calculate the DCI adjusted for esophageal body length (DCIa). DCIa was obtained by dividing DCI by the esophageal length (**d**).

of the EGJ on the 30 mm Hg isobaric contour plot (**Figure 1**). Swallows were characterized as normal (intact 30 mm Hg isobaric contour and a PFV < 8 cm/s), failed (complete failure of propagation without pressure domain above 30 mm Hg), hypotensive (≥2 cm defect on the 30 mm Hg isobaric contour), or rapidly conducted (PFV≥8 cm/s). The cutoff parameter of ≥2 cm on the isobaric contour was based on previous data supporting the fact that a 30 mm Hg wave front is associated with complete bolus transit (16,22).

The DCI, expressed as mm Hg s cm, was measured within the outlined space–time box that starts at the transition zone (topographic projection between striated and smooth muscle in the esophageal body) and extends distal to the proximal aspect of the EGJ and is bound temporarily at the end of peristalsis. DCI was calculated by multiplying the mean pressure in the space–time box above the 20 mm Hg isobaric contour by the length and duration of the space–time box. The DCI value was further adjusted to the esophageal body length by dividing the DCI value by the linear distance between the lower limit of upper esophageal sphincter and the upper limit of LES (**Figure 1**). The new variable named DCIa was assessed only when a propagation wave on the 30 mm Hg contour plot was present.

According to the peristaltic propagation pattern, patients were divided into five groups as follows: (1) peristaltic pattern—no failure of peristalsis on the 30 mm Hg isobaric contour and PFV < 8 cm/s in at least 8 out of 10 swallows, EGJ pressure within 10–35 mm Hg, and e-sleeve nadir relaxation < 15 mm Hg; (2) peristaltic dysfunction—failed peristalsis in ≥2 and ≤7 swallows or ≥2 cm defect on the 30 mm Hg isobaric contour; (3) esophageal spasm—PFV >8 cm/s in >2 out of 10 swallows; (4) aperistalsis—no continuous pressure domain above the 30 mm Hg isobaric contour on 10 out of 10 swallows, and EGJ relaxation; (5) achalasia—aperistalsis or spastic contractions on the distal esophagus, and impaired deglutitive EGJ relaxation on 10 out of 10 swallows (23).

Statistical analysis

The mean values of each variable of the HRM topography criteria in every patient were calculated and used for comparisons. Data are presented as median (interquatile range, minimum, maximum) of the mean values in the 30 patients. Statistical significance ($P < 0.05$) was assessed by the Mann–Whitney *U*-test during comparison of DCIa values between patients with and without peristaltic dysfunction.

RESULTS

Out of 31 patients, EHRM was well tolerated and a complete assessment of all segments of the pharynx and esophagus was possible in 30 patients. The median age was 10 years (range 6 months–15 years), 8 patients were under 5 years of age and 11 (36%) were boys. One 2-year-old patient did not tolerate the procedure with-

Table 1. Esophageal motility classification of 23 patients based on HRM topography criteria (16)

Parameter analyzed	*n*	Median	Minimum	Maximum	25th centile	75th centile
LES						
BP 10–35 mm Hg	24	22	8	32	15	30.5
BP >35 mm Hg	3	43	35	57	35	57
BP < 10 mm Hg	3	9	8	10	8	9
Relaxation (3 s nadir) >15 mm Hg	3	—	—	—	—	—
Peristalsis						
Peristaltic pattern						
DCI (mm Hg cm s)	15	2,710	1,969	4,296	2,311	3,149
DCIa (mm Hg s)	15	197.5	98.5	282.6	161.3	259.1
PFV (cm/s)		3.2	2.2	4.8	2.5	4.1
Peristaltic dysfunction						
DCI (mm Hg cm s)	12	630	349	2,116	392	1,041
DCIa (mm Hg s)	12	44.5	22.6	139.2	26.2	74.8
PFV (cm/s)		5.4	2.8	33.9	3.8	9.7
Spasm on consumption of solid food						
DCI (mm Hg cm s)	2	8,449	5,292	11,606	—	—
DCIa (mm Hg s)	2	413.1	231.1	591.2	—	—
PFV (cm/s)		20	8.0	37.3	11.15	28.5
Achalasia	3	—	—	—	—	—

BP, basal pressure; DCI, distal contractile integral; DCIa, distal contractile interval adjusted for esophageal length; PFV, pressurization front velocity.

out sedation. Overall, patients older than 5 years of age had a better tolerance of the procedure compared with younger ones.

A total of 293 wet swallows and 63 solid swallows were analyzed. The parameters analyzed are shown in **Table 1**. The esophageal motor findings were as follows: normal peristalsis ($n=15$), peristaltic dysfunction ($n=12$), achalasia ($n=3$), and spasm on consumption of solid food ($n=2$). DCIa of patients with peristaltic dysfunction (median 44.5 mm Hg s, range 22.6–139.2) was significantly lower than that of patients without peristaltic dysfunction (median 197.5 mm Hg s, range 98.5–282.6), $P<0.001$ (**Figure 2**).

Out of 22 patients who underwent MRS, 15 with normal peristalsis and 7 with a peristaltic dysfunction showed a lack of peristaltic propagation during the sequence of swallows and complete relaxation of EGJ, followed by a sequence of propagated contraction in the distal esophagus. Out of 7 patients with peristaltic dysfunction, 1 showed complete aperistalsis and complete EGJ relaxation, probably because of severe esophageal dysmotility in association with severe esophagitis (**Figure 3**). Three patients with achalasia had aperistalsis with a lack of EGJ relaxation during the sequence of MRS; one of them had an increasing pan-esophageal intrabolus pressure that culminated in a vigorous spasm of the esophageal body after the sequence of MRS. At that moment, esophageal shortening as a consequence of a spasm of the esophageal body was observed without EGJ relaxation. A "pseudorelaxation" of LES

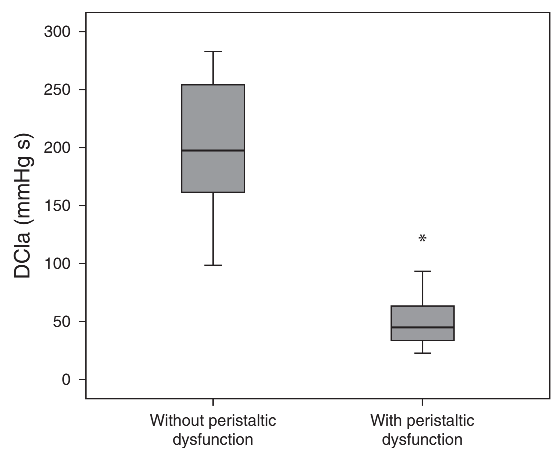

Figure 2. The distal contractile integral adjusted for esophageal body length (DCIa) of patients submitted to high-resolution manometry. Median values are represented by horizontal bars. *DCIa of patients with peristaltic dysfunction was significantly lower than that of patients without peristaltic dysfunction ($P<0.05$).

was observed on the channels that previously recorded LES (**Figure 3**). A patient with vigorous achalasia showed simultaneous contractions (spasm) in the distal esophagus accompanied by esophageal shortening and "pseudorelaxation" on MRS sequence (**Figure 4**).

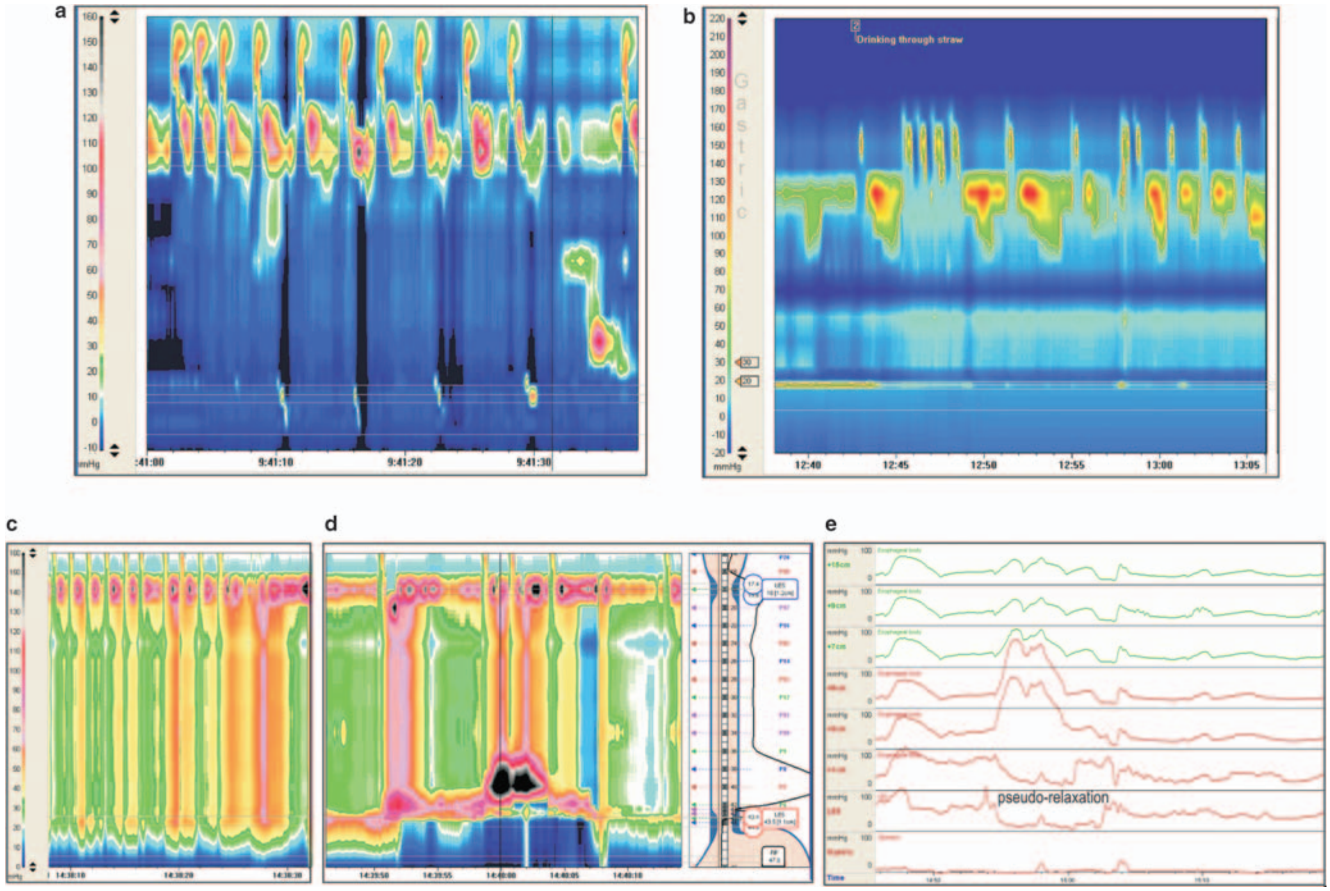

Figure 3. Esophageal high-resolution manometry (EHRM) of a sequence of multiple rapid swallows (MRS). Absence of peristalsis followed by complete lower esophageal sphincter (LES) relaxation was observed both in patients without dysphagia (**a**) and in those with severe peristaltic dysfunction (**b**). In contrast, a pan-esophageal intrabolus pressure associated with a lack of LES relaxation was observed in achalasia patients (**c**). By the end of the sequence of MRS, an episode of esophageal spasm with esophageal shortening and a high-pressure LES without relaxation was observed (**d**). A close view of the area marked with the black semicircle resembles an LES "pseudorelaxation" that is clearly seen on the two bottom channels, indicating catheter movement as a consequence of esophageal shortening (**e**).

Of the 30 patients, 21 consumed solid food during the EHRM procedure. Only two patients who had a previous symptom of dysphagia on consumption of solid food had a pattern of esophageal spasm associated with food impaction in the chest when solid food was tested. Both patients had no EHRM abnormalities on standard wet swallows. A 15-year-old patient, who had an underlying autoimmune disease and poor response to immunosuppressive therapy, had the feeling of having the "food stuck" in the mid-thorax while swallowing solids on EHRM. Manometry showed a spasm in the mid-to-distal esophagus (**Figure 4**) and a simultaneous fluoroscopy showed the contrast "stuck" in the mid-distal esophagus. Another 16-year-old patient, who had a previous Heller's myotomy and fundoplication at 1 year of age, also complained of chest pain, and EHRM showed a spasm in the distal esophagus (**Figure 4**).

DISCUSSION

This study illustrates the use of EHRM in a pediatric age group while using a standardized protocol and analytical method. Despite the inherent limitations of the pediatric population, it introduced a new protocol in unsedated children in the context of a clinical setting, moving from research into clinical application. The ability to analyze data using spatiotemporal plots normalized to gastric baseline pressure eliminates a great deal of motion artifacts, which previously required many children to be sedated for the procedure.

In this study, the addition of a sequence of MRS with swallowing intervals of less than 4 s and solid swallows in unsedated patients has proven helpful in clarifying esophageal physiology in cases in which diagnosis was uncertain using sedated conventional manometry. For example, MRS can help to differentiate aperistalsis due to severe ineffective esophageal motility (IEM) from aperistalsis due to achalasia; and solid swallow can help to highlight some motility abnormalities that were not observed on previous standard wet swallows, e.g., esophageal spasm.

MRS is a stimulus known to inhibit motility in the esophageal body of healthy subjects but not in patients with simultaneous esophageal contractions (24). Swallowing at intervals of <4 s inhibits the peristaltic wave from reaching the distal esophagus and induces complete LES relaxation (25,26). In achalasia, the early

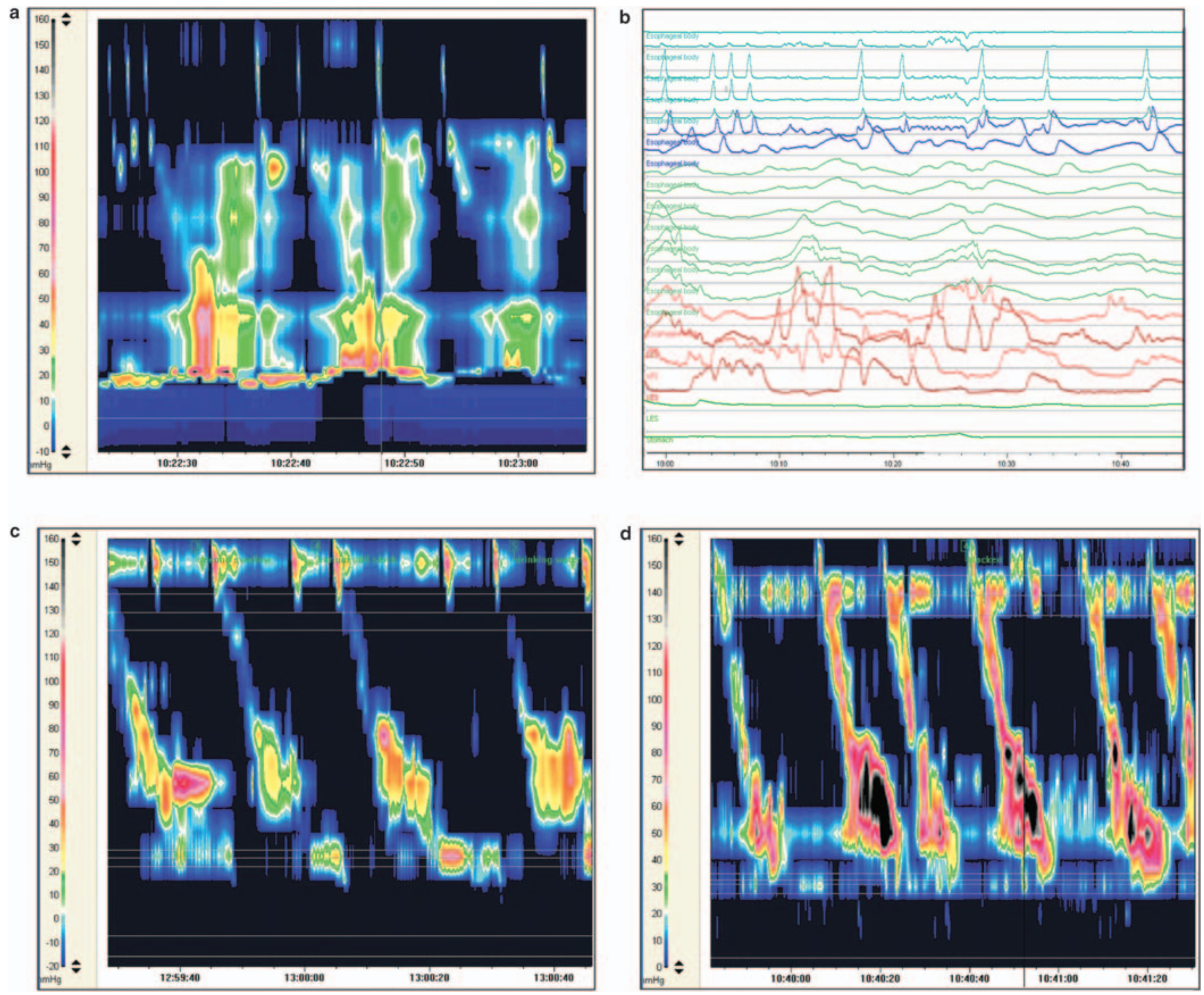

Figure 4. Esophageal shortening after a sequence of MRS was observed in a patient with vigorous achalasia. Simultaneously propagated waves on the contour plot above 30 mm Hg were observed on the distal esophagus (**a**, **b**). On solid swallows, two patients who had a history of dysphagia on consumption of solid food showed spasm with high-velocity contraction waves in the mid-to-distal esophagus (**c**, **d**). Both patients had no abnormalities on previous standard esophageal high-resolution manometry (EHRM) wet swallows.

arrival of a simultaneous wave may prematurely close the LES, thus preventing its relaxation (27), which is likely to be a consequence of nerve damage and disruption of neural pathways (28). MRS (free drinking) of more than 100 ml of water is recommended, as it increases the sensitivity to LES dysfunction (9). This was useful in the clarification of pathophysiology in patients with aperistalsis, in which the LES relaxation pattern was targeted, allowing us to differentiate patients with aperistalsis due to severe IEM from patients with aperistalsis due to achalasia. On conventional manometry, it is often difficult to differentiate patients with achalasia from those with severe IEM, given reports of normal LES relaxation in the former (29). However, using EHRM, such "normal" LES relaxation in patients with achalasia has been shown to reflect "pseudorelaxation" due to an esophageal shortening and a consequent movement of LES upward (9,30).

A high amplitude of esophageal body contraction following a sequence of MRS has been previously described in adults (26). It was evident on HRM recordings in most of our children with a normal LES, although standardization of the MRS protocol to within the tight confines used in adult manometric practice proved impossible in some of the age ranges studied. In pediatric practice, we considered it much more relevant to study LES inhibition by MRS to exclude achalasia and achalasia-like conditions.

In this study, in contrast to other children with dysphagia, two patients had a specific complaint of food impaction accompanied by chest pain while consuming solids. Both had esophageal spasm on consumption of solids that was not observed on previous EHRM with wet swallows. In one patient, combined fluoroscopy confirmed the food impaction. The additional use of solid swallow has been described in adults to diagnose esophageal spasm in patients with dysphagia who underwent normal conventional manometry (31). This is the first study to describe its usefulness in pediatric patients. Further studies are needed to determine normal patterns of esophageal solid bolus transit in children, given the finding that healthy adults may need more than one swallow to clear solid boluses from the esophagus, and that subjects have poor perception of whether such boluses cleared the esophagus on any given swallow (32).

Ethical constraints limited the acquisition normative data from asymptomatic (unsedated) children. We therefore classified esophageal motility disorders using the HRM criteria developed for adults (16)—data that we show can be applied to children. The HRM data that we present does correlate with accepted and published standards of normality for conventional pediatric esophageal manometry in which the parameters in question are expected to be normal because the pathology is elsewhere within the esophagus (previous normative data mainly describe LES basal pressure within the 10–35 mm Hg range, and primary peristaltic propagation pattern expected in 82% of swallows)(33–35). Similarly, we were able to use the normal esophageal body peristaltic pattern observed in patients with primary abnormalities of the LES as an internal reference against which to validate the DCI measurement in patients with hypoperistalsis.

DCI was measured following the same parameters in adults; however, it was adjusted to esophageal body length. On a three-dimensional view, DCI would be the volume of the solid spanning from the base to its peak and is measured along the entire esophageal segment between the transition zone and LES (16). It is therefore essential that DCI be normalized for esophageal length. It was decided to use the total length of the esophagus as a denominator rather than the length distal to the transition zone because of difficulties in defining the transition zone in patients with peristaltic dysfunction.

The use of the DCI cutoff value has been described in adults for the definition of hypertensive contraction and the DCI lower limit has not been considered (16). This study suggests that the lower DCI limit might be important for the interpretation of hypotensive contraction. High DCI values were not found in this study because of the predicted low prevalence of hypertensive contraction (nutcracker esophagus) in children. Conversely, lower DCIa values were observed in this study and they were significantly lower in patients with peristaltic dysfunction than in those without peristaltic dysfunction. Moreover, this finding might reflect a chronic bolus escape associated with a wide separation of the proximal and distal contraction waves and a reduced contractile force within the transition zone that would be found, e.g., in patients with IEM (12). Thus, this study introduced the new parameter DCIa, which may be useful for the assessment of hypotensive peristalsis in patients with peristaltic dysfunction.

On the basis of all the issues presented above, we advocate that children should ideally not be sedated for EHRM and should adhere to the following protocol: (i) identify LES using standard manometry tracing if necessary (ii); run a baseline recording of LES pressure, allowing for an initial 3 min "settling down" period. Once all relevant structures are identified, (iii) perform (a) wet swallows—10 swallows at a minimum of 20 s intervals of 0.5–5.0 ml, aiming for the maximal tolerated volume (5 ml), 5.0 ml for those older than 5 years of age, 2.0 ml for those under 5 years, 0.5–1.0 ml for infants, and consider wet swallows unsafe in patients with oropharyngeal dysphagia, (b) check MRS offering about 100 ml of liquid by means of a straw or a bottle (increases sensitivity to LES dysfunction, e.g., intrabolus pressure is high in achalasia), (c) consider solid swallows if the patient has symptoms triggered by the consumption of solid food (increases diagnostic sensitivity and clinical significance of manometric findings), preferably test the triggering solid food or at least one slice of toast in subsequent amounts of 2×3 cm in size. This protocol is adapted from that recommended in adults (9) and is expected to fit into the pediatric age, provided appropriate suggestions are followed.

In conclusion, this study provided objective information regarding topography pressure parameters of esophageal motility in children that may contribute to a standardized protocol for performance and analysis of EHRM in children. Conventional analytical methods and the new DCIa variable may be useful to further clarify paradigms regarding the pathophysiology of motility abnormalities and consequently improve the diagnosis of pediatric esophageal motility disorders.

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CONFLICT OF INTEREST

Guarantor of the paper: Keith J. Lindley, MD, PhD.
Specific author contributions: Helena A.S. Goldani conducted the study, analyzed the data, and drafted the paper. Annamaria Staiano helped design the study. Osvaldo Borrelli independently analyzed the data. Nikhil Thapar revised the paper. Keith J. Lindley designed and conducted the study and revised and produced the final draft of the paper.
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Potential competing interests: None.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Esophageal high-resolution manometry (EHRM) is a new test well established in adults.
- ✓ There is no standardized protocol for EHRM in children.

WHAT IS NEW HERE

- ✓ A new standardized protocol for EHRM in children is presented.
- ✓ Adaptation of some EHRM parameters is needed for children.

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