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New Insights in Gastroesophageal Reflux, Esophageal Function and Gastric Emptying in Relation to Dysphagia Before and After Anti-Reflux Surgery in Children

M. J. Smits · C. M. Loots · M. A. Benninga · T. I. Omari · M. P. van Wijk

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Abstract In children with gastroesophageal reflux (GER) disease refractory to pharmacological therapies, anti-reflux surgery (fundoplication) may be a treatment of last resort. The applicability of fundoplication has been hampered by the inability to predict which patient may benefit from surgery and which patient is likely to develop post-operative dysphagia. pH impedance measurement and conventional manometry are unable to predict dysphagia, while the role of gastric emptying remains poorly understood. Recent data suggest that the selection of patients who will benefit from surgery might be enhanced by automated impedance manometry pressure-flow analysis (AIM) analysis, which relates bolus movement and pressure generation within the esophageal lumen.

Keywords Children · Gastroesophageal reflux disease · Fundoplication · Dysphagia · AIM analysis

Abbreviations

AIM analysis	Automated impedance manometry analysis
GER	Gastroesophageal reflux
GERD	Gastroesophageal reflux disease
HRM	High resolution manometry
LES	Lower esophageal sphincter
MII	Multichannel intraluminal impedance
NadImp	Nadir impedance
PeakP	Peak pressure
pH-MII	Combined pH and multichannel intraluminal impedance
P-NadImp	Pressure at the time of NadImp
PPI	Proton pump inhibitor
TLESR	Transient lower sphincter relaxation

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M. J. Smits · C. M. Loots · M. A. Benninga (✉) · M. P. van Wijk
Department of Pediatric gastroenterology and Nutrition, Emma Children's Hospital, AMC, Amsterdam, The Netherlands
e-mail: m.a.benninga@amc.uva.nl

T. I. Omari
Centre for Paediatric and Adolescent Gastroenterology, CYWHS, Women's and Children's Hospital, Adelaide, SA, Australia

T. I. Omari
School of Paediatrics and Reproductive Health, University of Adelaide, Adelaide, SA, Australia

Gastroesophageal Reflux Disease and Treatment in Children

Gastroesophageal reflux disease (GERD) in children is common, affecting approximately 12 % of infants up to 12 months and 1 % of older children [1]. GERD is clinically diagnosed when gastroesophageal reflux (GER) causes troublesome symptoms [2]. In infants, GERD is often mild and short-lived, with >90 % of patients being free symptoms at the age of 18 months [2, 3].

When there is no endoscopic evidence of esophagitis, GERD can be challenging to treat. Standard treatment consists firstly of conservative measures: lifestyle changes, excess weight reduction, and avoidance of tobacco smoke exposure. In specific cases, allergies are associated with GER symptoms, and avoidance of allergens may relieve symptoms. If pharmacological therapy is considered, very few evidence-based options are available. Proton pump inhibitors, while effective in adults, do not reduce GER symptoms in infants and no evidence is available for their effectiveness in older children [4]. Prokinetic agents are sometimes considered, but randomized controlled trials have thus far not convincingly shown any benefit over placebo in children nor adults [5, 6].

The lack of therapeutic efficacy of acid suppressive therapy and prokinetic agents might be explained by the fact that these do not target the underlying mechanism of reflux, i.e. transient lower sphincter relaxation (TLESR) [3, 7]. Although new drugs aiming to reduce TLESRs are being developed for adults [especially GABA(B) agonists and mGLUR5 antagonists] [7, 8], these have many side effects and are only sporadically tested in children [8, 9].

In patients with objective evidence of acid-related GERD, based on upper endoscopy, pH-metry and/or pH impedance measurement (pHMII), who experience severe symptoms or have esophagitis refractory to optimal medical therapy, anti-reflux surgery (fundoplication) may be a treatment of last resort [10].

Indications for fundoplication are poorly defined in children [11, 12], and there is no uniformity between hospitals in the approach to these infants and children [13]. Neurologically impaired children, children with a history of esophageal atresia, and children with respiratory alarm symptoms considered GERD-related (e.g., apnea, bronchiectasis, recurrent pneumonia) are more prone to undergo fundoplication [14].

Fundoplication Techniques

The primary goal of anti-reflux surgery is to reduce GER without preventing passage into the stomach of swallowed substances. Different types of fundoplication have been developed by Nissen (360° fundic wrap around the esophagus), Thal and Toupet (both partial wraps) (see Fig. 1). These traditionally open procedures are now more commonly performed laparoscopically. A recent study in children by Knatten et al. did not find differences in terms of complications during 30 days follow-up comparing open and laparoscopic Nissen fundoplication; however, the complication rate was high (50 % in both groups) [15]. Laparoscopic fundoplication in children is superior to the open procedure in terms of length of hospital stay and in hospital mortality. There appears to be no advantage of one over another in terms of costs, as cost–effectiveness balances between longer duration of surgery in open fundoplication versus higher instrumental cost in laparoscopically surgery [16].

In adults, it has been established that, compared to Nissen fundoplication, laparoscopic partial fundoplication causes less dysphagia, gas bloating, and redo surgeries [16–18]. Similar to adult findings, pediatric studies suggest that, while total and partial fundoplication produce equivalent GER control in children [19•], dysphagia may occur less frequently in partial versus total fundoplications [20]. These conclusions are, however, based on limited data and uncertainty remains with respect to the optimal fundoplication technique. In addition, prospective evidence is limited in terms of efficacy and complication rates between partial and total fundoplication [19•].

Efficacy and Safety of Fundoplication

Efficacy and safety of fundoplication in children is poorly investigated. Success rates, in terms of complete relief of symptoms <6 months after surgery, of 57–100 % in neurologically normal and 57–79 % in neurologically impaired children are reported [19•].

Overall complications during and after fundoplication in children occur in 0–54 %, varying from post-operative dysphagia to wound infection and perforation [19•, 21•]. Post-operative dysphagia is the most common complication, occurring in 0–33 % of patients in the first months after fundoplication [17]. Recently, Schneider et al. retrospectively assessed a group of 288 children who underwent Nissen fundoplication [21•]. In this study, 24 % of patients required lower esophageal dilation because of dysphagia. Long-term follow-up studies (up to 5.5 years) report treatment failure (relapsing GERD) in 1 % of non-neurologically impaired children and 12 % in neurologically impaired children [22].

Patient Selection for Fundoplication

The applicability of fundoplication has been hampered by the inability to predict which patient may benefit from surgery and which patient is likely to develop complications. We will discuss current evidence for patient selection for fundoplication based on assessment of GER parameters, esophageal motility, and gastric emptying. We will focus more in depth on the use of a novel pressure-flow analysis technique to identify esophageal motility parameters that are associated with post-operative complications such as dysphagia.

pH and pHMII GER Parameters

In children, fundoplication has been shown to significantly decrease esophageal acid exposure at short term follow up [23–26]. Multiple adult studies have shown that patients who have abnormal pH-metry and pHMII findings preoperatively are most likely to benefit most from fundoplication [27–29]. This experience is not easily translated to the pediatric setting, where pH-metry and pHMII-based symptom association is harder to apply. In children, Rosen et al. used pHMII to predict fundoplication outcome. They found no GER parameter or symptom association indices prior to surgery to be able to predict post-operative improvement or complications [30].

Recently, we compared pre- and post-operative pHMII results in 10 pediatric patients [31••]. The mean number of GER episodes, acid exposure, and impedance baseline values based on 24-h pHMII monitoring were significantly reduced after surgery. Nevertheless, none of the GER parameters were

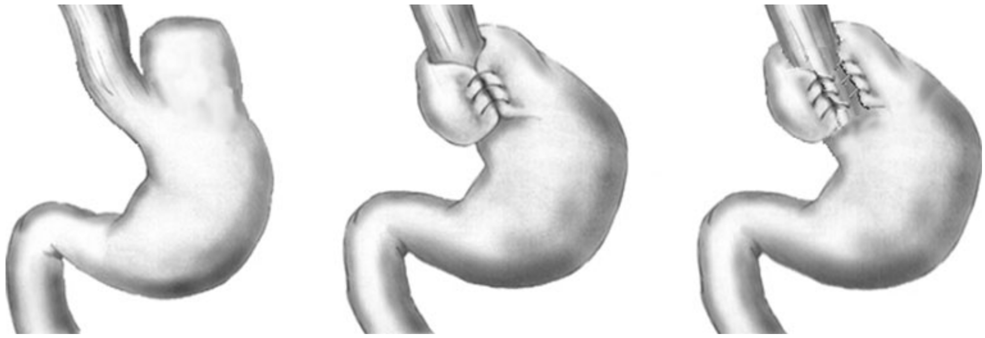

Fig. 1 Different types of fundoplication. *Left* Normal anatomy of esophagus, stomach and duodenum. *Middle* Complete fundoplication: the gastric fundus is completely wrapped around the lower end of the esophagus. *Right* Partial fundoplication: the gastric fundus is partially wrapped around the lower end of the esophagus

able to predict outcome of surgery, either in terms of success or complications such as dysphagia.

Esophageal Motility

Conventional and High Resolution Manometry

Several studies have evaluated esophageal manometry and esophago-gastric junction characteristics in an attempt to predict complications by determining pressure variables [25, 27, 31••, 32]. Published studies in adults have found that pre-operative lower esophageal sphincter (LES) resting pressure, residual LES relaxation pressures, intrabolus pressures, and distal peristaltic amplitude are poor predictors of post-fundoplication dysphagia [33–39].

The golden standard for evaluation of esophageal motility is shifting from conventional manometry to high resolution manometry (HRM). In a HRM catheter, pressure sensors are spaced in close proximity (e.g., 1–2 cm apart), allowing a more detailed view of intraluminal pressure activity than conventional manometry. A standard HRM study comprises of, like conventional manometry, a series of ten 5-mL swallows administered in supine position. In adults, HRM has been used to formulate a practical classification of esophageal motility disorders, the Chicago classification [40•]. These are based on special developed metrics, each characterizing a specific feature of deglutitive esophageal function. Every single swallow is individually judged, and a summary of that analysis for all ten swallows is then utilized to fit criteria and result in a manometric diagnosis. One of the key metrics in HRM is the Integrative Relaxation Pressure, which integrates the lowest 4s of EGJ pressure over 10s of LES relaxation from initiation of a swallow.

Chicago metrics have not yet been thoroughly studied as predictors of post-fundoplication dysphagia. A higher Integrative Relaxation Pressure has been found in patients with compared to patients without post-operative dysphagia. Nevertheless, pre-fundoplication HRM measurements were lacking [41]. Taking a different approach, pre-fundoplication abnormal response to multiple rapid swallows have been associated with late post-operative dysphagia in adult patients [42••]. Multiple rapid swallow analysis might thus be a useful tool to pre-operatively assess the risk for post-operative dysphagia in adults. However, correct administration and analysis of multiple rapid swallows in children, especially the young and neurological impaired, is extremely challenging. Although HRM in pediatric clinical practice is increasingly performed in children and first results of use in clinical practice are promising [43, 44], its use before and after fundoplication assessment remains to be investigated.

AIM Analysis of Combined MII and Manometry

Recently, a new approach which integrates pressure and impedance measurements, called automated impedance manometry pressure-flow analysis (or AIM analysis), was developed, initially for the evaluation of pharyngeal swallowing, where it has greatly enhanced the clinical utility of impedance-manometry [45–49].

Using a similar approach, Myers et al. examined a range of esophageal AIM variables (see Fig. 2) for potential associations with the occurrence of esophageal dysphagia in adults [50••]. They identified three variables linked to dysphagia: intrabolus pressure, intrabolus pressure slope, and TNadImp-PeakP (time between nadir impedance to peak pressure). These variables were combined to derive the Dysphagia Risk Index (also called the Pressure Flow Index), which appears to demonstrate a high degree of prognostic value for prediction of post-operative new-onset dysphagia [51••].

We evaluated post-operative dysphagia by means of the AIM analysis in 10 children (range 1.1–17.1 years) before and after laparoscopic anterior partial fundoplication measuring pHMII and manometry. None of the conventional manometry parameters (peak pressure, peristalic contractions, LES resting pressure, LES nadir pressure, bolus transit time) were different, comparing patients with and without dysphagia. In addition, in none of the 10 children, did conventional parameters differ before and after fundoplication, except for a significant decline in complete LES relaxations after surgery. The pre-operative dysphagia risk index calculated based on the algorithm designed by Myers et al. was

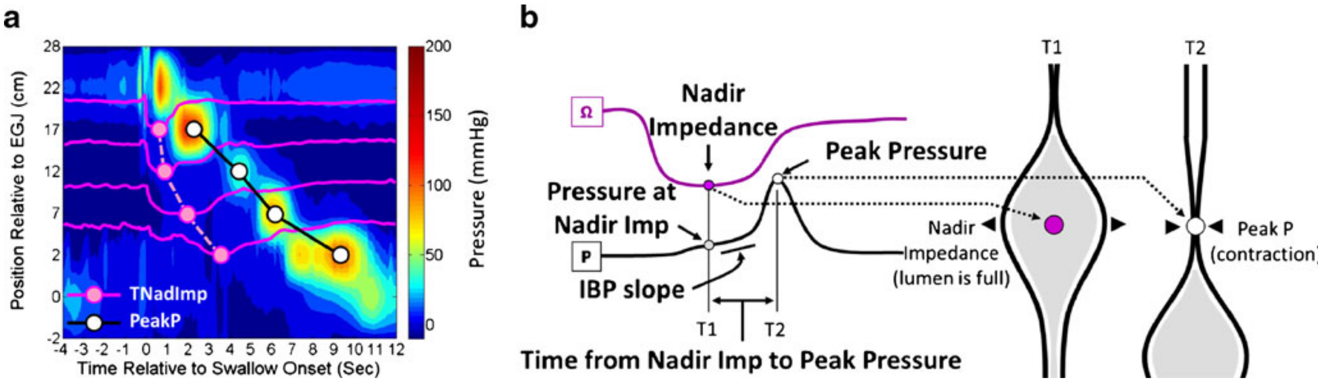

Fig. 2 Calculation of esophageal pressure-flow variables in AIM analysis. *Left* An esophageal pressure topography plot showing pressure (color iso-contours) and impedance (*purple lines*) changes during swallowing of a 5-ml viscous bolus in a control subject. *Circles* and *lines* indicate the timing of Nadir Impedance and Peak Pressure. *Right* The essentials of AIM pressure flow analysis based on timing of nadir impedance (*T1*) and peak pressure (*T2*)

significantly higher in patients with post-operative dysphagia (*n*=4) compared to those without post-operative dysphagia (*n*=6). This was the first study to apply AIM analysis in a prospective study on fundoplication in children [31••].

Gastric Emptying

The role of gastric emptying in GERD remains poorly understood. Delayed gastric emptying has been associated with GER disease [52]; nevertheless, promotility agents do not reduce GER symptoms in adults or children [5, 6].

With regards to fundoplication, it seems fairly well established in adult patients that fundoplication increases gastric emptying rate [29, 53]. The relationship between delayed gastric emptying and complications after fundoplication in children and adults is less clear cut. Delayed gastric emptying has been reported to adversely influence outcome of surgery [54, 55]. However, a large prospective trial observed no relationship between gastric emptying and outcome of surgery [56]. A recent study evaluated 11 children before and after fundoplication with gastric emptying scintigraphy. Similar to previous and adult studies, gastric emptying was found to significantly accelerate after surgery. However, since pre-operative gastric emptying did not predict post-operative outcome, the authors suggest that gastric emptying is unnecessary in the work up for fundoplication [57].

We determined gastric emptying in ten children before and after fundoplication, and observed that the four patients who developed post-operative dysphagia had a longer gastric emptying half time compared to the patients who did not [31••]. The literature is inconsistent on this issue and the pathophysiology of the interaction between gastric emptying, GERD, and post-operative dysphagia requires further study.

Summary and Future Perspectives

Fundoplication is the third most commonly performed pediatric surgical procedure, but with a high complication rate, up to 33 %. One should carefully weigh the risk of complications against the chance of success in target patients.

Medical therapy for GERD in children is not optimal, and although new therapeutic approaches are being investigated in adults, they will not be available for children in the near future. Therefore, fundoplication will remain a radical but in rare cases (reflux-associated life-threatening events) necessary option in the pediatric population.

There is a clear need for functional measures that assist decision making in relation to anti-reflux surgery in children. The Chicago classification for motility disorders in adults is not available for children. In addition, it is still unclear whether Chicago metrics are able to predict post-fundoplication dysphagia prior to surgery. New data suggest that the applicability of fundoplication, and the selection of patients who will benefit from surgery, might be enhanced by a new analysis method that integrates pressure (manometry) and flow (MII), and derives a dysphagia risk index, which relates bolus movement and pressure generation within the esophageal lumen. This contrasts with the standard methods of separate analysis of manometry and impedance, which do not predict post-operative outcome.

Larger trials are needed to determine the clinical relevance in terms of the prognostic value of this new analysis approach. These trials should also include the assessment of gastric emptying prior to and post-surgery, since the relationship between delayed gastric emptying and complications after fundoplication is still not clarified.

Conclusion

Recent developments in the assessment and analysis of esophageal and gastric motility may enable us to better predict the risk of post-operative complications in the future. This development is essential for careful selection of pediatric patients with refractory GERD for fundoplication.

Take Home Messages

- pH impedance and conventional manometry are unable to predict post-operative dysphagia
- AIM analysis combines impedance and manometry values to derive a Dysphagia Risk Index
- The Dysphagia Risk Index seems to be able to predict post-operative dysphagia in both adults and a pilot study of 10 children
- Larger trials are needed to confirm clinical relevance of AIM analysis in predicting post-operative dysphagia in children

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Compliance with Ethics Guidelines

Conflict of Interest M.J. Smits, C.M. Loots, M.A. Benninga, T.I Omari, and M.P. van Wijk declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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