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Gastroesophageal reflux, esophageal function & gastric emptying in relation to dysphagia before & after anti-reflux surgery in children

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Abbreviations

AIM analysis	Automated impedance manometry analysis
DRI	Dysphagia risk index
GE	Gastric emptying
GEBT	Gastric emptying breath test
GER	Gastroesophageal reflux
GERD	Gastroesophageal reflux disease
LES	Lower esophageal sphincter
MII	Multichannel intraluminal impedance
NadImp	Nadir impedance
NI	Neurologic impairment
P-NadImp	Pressure at the time of NadImp
PeakP	Peak pressure
pH-MII	Combined pH and multichannel intraluminal impedance
TLESR	Transient lower esophageal sphincter relaxation

Introduction

Gastroesophageal reflux disease and treatment in children

Gastroesophageal reflux disease (GERD) in children is common, it affects approximately (?)3% of infants and <1% of older children.[1] GERD is clinically diagnosed when gastroesophageal reflux (GER) causes troublesome symptoms, and is a source of stress for both patients and caregivers. In infants, GERD is often mild and short lived, with >90% being free of GERD symptoms at the age of 18 months.[2,3]

'Symptomatic GERD', that is a clinical diagnosis of GERD without corroborative evidence such as endoscopic evidence of esophagitis, can be challenging to treat. Standard treatment consists firstly of conservative measures: lifestyle changes, excess weight reduction, no exposure to tobacco smoke. In specific cases allergies are associated with GERD, and avoidance of allergens may relieve symptoms. If pharmacological therapy is considered, acid suppression is the first choice and using proton pump inhibitors (PPIs) is favored above H2-antagonists and on demand buffering agents.[2] However, acid suppression therapy in infants and children is now widely discouraged as PPIs, whilst proven effective in increasing gastric pH, do not reduce GERD symptoms.[4]

The lack of therapeutic efficacy of acid suppressive therapy might be explained by the fact that acid suppression does not target the underlying mechanism of reflux which is transient lower sphincter relaxation (TLESR).[3,5] Acid suppression only turns acid GER into weakly acid GER, which may still cause troublesome symptoms. Although other therapeutic agents are being developed for adult GERD treatment (especially GABA(B) agonists and mGLUR5 antagonists), these have many side effects and are not yet tested in children.[6,7] Therefore, no pharmacological interventions aimed a reducing TLESRs are available.

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.[8]

Indications for fundoplication are poorly defined in children[2,9,10] and there is no uniformity between hospitals in the approach to infants and children with pharmacological therapy resistant GERD.[11] Neurologically impaired children, children with a history of esophageal atresia[12] and children with respiratory alarm symptoms considered GERD-related (e.g. apnea, bronchiectasis, recurrent pneumonia) are more prone to undergo fundoplication.

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), figure 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 very high (50% in both groups). [13] The laparoscopic procedure in children has been shown to be 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, cost-effectiveness balances between longer duration of surgery in open fundoplication versus higher instrumental cost in laparoscopically surgery.[14,15]

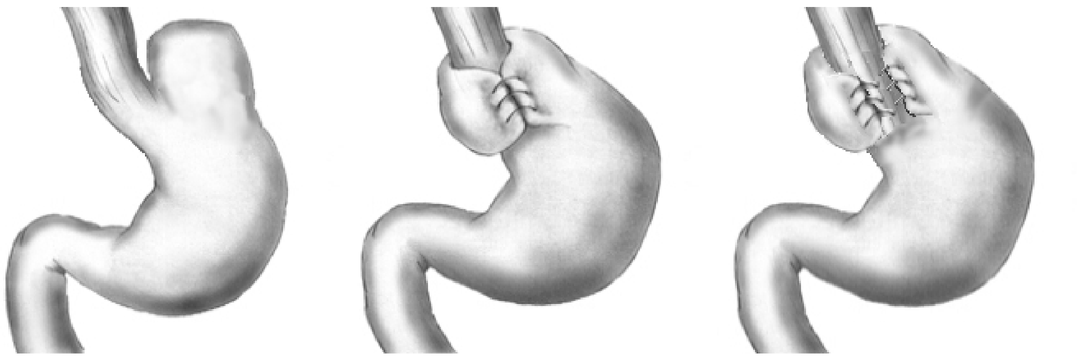

Figure 1. Different types of fundoplication. A. normal anatomy B. Complete fundoplication C. partial fundoplication

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 observations suggested that 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 remains poorly investigated. Success rates in terms of complete relief of symptoms <6 months after surgery of 57-100% (median 86%) have been suggested.[19] In neurologically impaired children, success rates are lower, varying from 57-79% (median 70%).[19]

Overall complications during and after fundoplication in children occur in 0-54%, varying from postoperative 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.[16] Recently, Schneider et al retrospectively assessed a group of 288 children who underwent Nissen fundoplication. [21] In this study 24 percent 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]

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 including dysphagia 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.

GER parameters before and after fundoplication

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 have 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, nor symptom association indices such as positive Symptom Index or Symptom Sensitivity Index prior to surgery to be able to predict post operative improvement or complications. [30]

Recently, we compared pre and postoperative pHMII results in 10 pediatric patients.[31] The mean number of GER episodes, acid exposure and impedance baseline values based on 24hr pHMII monitoring were significantly reduced after surgery. Nevertheless, none of the GER parameters were able to predict outcome of surgery neither in terms of success nor complications such as dysphagia.

Esophageal motility before and after fundoplication

Several studies have evaluated esophageal manometry and esophago-gastric junction characteristics in an attempt to predict complications by determining pressure variables[26,27,31,32]. Published studies in adults have found that pre-operative lower esophageal sphincter (LES) resting, 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 (eg 1-2 cm apart) allowing a more detailed view of intraluminal pressure activity than conventional manometry, with only 5-8 pressure sensors per catheter. A Standard HRM study comprises, like conventional manometry, of a series of ten 5mL swallows administered in supine position. In adults, HRM derived metrics have been used to formulate a practical classification of esophageal motility disorders, the Chicago classification. [40] Chicago classifications are based on special developed metrics, each characterising 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. On of the key metrics in HRM is the Integrative Relaxation Pressure (IRP) , which integrates the lowest 4 secs of EGJ pressure over during ten seconds 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 (IRP) has been found in patients with post surgery dysphagia compared to patients without postoperative dysphagia. Nevertheless, pre fundoplication HRM measurements were lacking. [41] Taking a different approach, pre fundoplication abnormal response to multiple rapid swallows (MRS), have been associated with late postoperative dysphagia in adult patients. [42] MRS thus may be a useful tool to pre operatively assess the risk for post operative dysphagia in adults. However, correct administration and analysis of MRS in children, especially the young and neurological impaired, is challenging. Although HRM in pediatric clinical practice is increasingly performed in children and first results of use in clinical practice are promising [43,44], however the use of it in before and after fundoplication assessment remains to be investigated.

Recently, a new approach which integrates pressure and impedance measurements, called automated impedance manometry pressure-flow analysis (or AIM analysis), has demonstrated promising results for predicting post-operative dysphagia. [31,45,46]

AIM analysis combines pressure and impedance recordings to objectively derive oesophageal pressure-flow variables. The time of peak pressure (PeakP) & nadir impedance (NadImp) are reference points identified by software algorithms that define: time between nadir impedance and peak pressure (TNadImp-PeakP), pressure at nadir impedance (PNadImp), peak pressure (PeakP), median intra-bolus pressure (IBP) & IBP slope *(see figure 2)*.

Figure 1. *Calculation of pressure-flow variables in AIM analysis*

A. Impedance-manometry assembly. B. Swallow on conventional impedance (top 6 channels) and manometry (bottom 8 channels). C. Combined impedance-manometry plot of a swallow at one point in the esophagus. The time between the point of nadir impedance and peak pressure (TNadImp-PeakP), the intra bolus pressure (IBP) and the intra bolus pressure slope (IBP-slope = time from IBP to $T_{1/2}$, dotted line) are calculated.

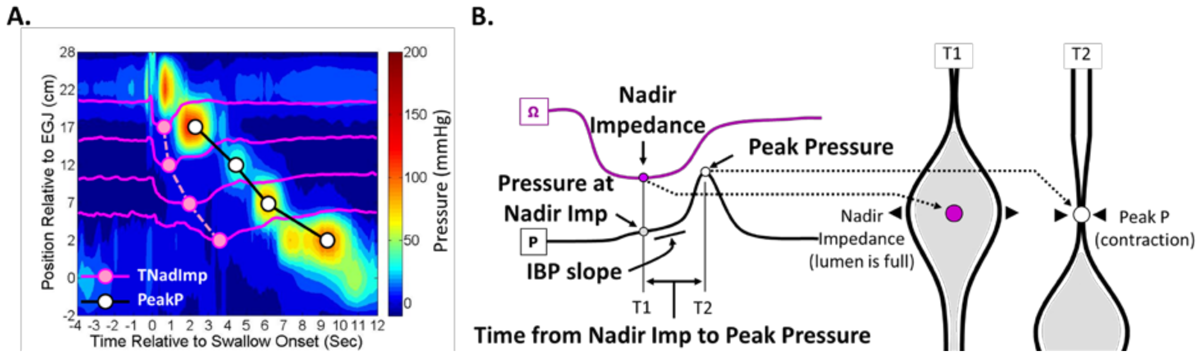

Figure 1. *Calculation of esophageal pressure-flow variables in AIM analysis.*

A. An esophageal pressure topography plot showing pressure (colour 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.

B. The essentials of AIM pressure flow analysis based on timing of nadir impedance (T1) and peak pressure (T2).

AIM analysis was initially developed for evaluation of pharyngeal swallowing, where it has greatly enhanced the clinical utility of impedance-manometry. Using pharyngeal AIM, deglutitive function can be assessed using the swallow risk index (SRI).[47,48] The SRI is a global measure of swallow effectiveness and aspiration risk derived through the combination of AIM variables associated with the occurrence of deglutitive aspiration on videofluoroscopy and has recently been proven have clinical utility for assessing deglutitive aspiration risk to liquid boluses in adult patients.[49-51]

Using a similar approach, Myer's et al. examined a range of esophageal AIM variables for potential associations with the occurrence of esophageal dysphagia in adults.[45] They identified three variables linked to dysphagia: intrabolus pressure (IBP), IBP slope and TNadImp-PeakP (time between nadir impedance to peak pressure). These variables were combined to derive the Dysphagia Risk Index (DRI, also called the Pressure Flow Index (PFI)), which appears to demonstrate a high degree of prognostic value for prediction of post operative new-onset dysphagia.[46]

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, conventional parameters differed before and after fundoplication, except for a significant decline in complete LES relaxations after surgery.[31] The pre operative dysphagia risk index (DRI) calculated based on the algorithm designed by Myers et al was significantly higher in patients with postoperative dysphagia (n=4) compared to those without postoperative dysphagia (n=6).

This was the first study to apply AIM analysis in a prospective study on fundoplication in children. The results of this study are in accordance with previously performed adult studies, where esophageal AIM analysis is proven accurate and pharyngeal AIM analysis is validated as a clinical tool to assess pharyngeal swallow effectiveness and risk for aspiration. [45-48]

Delayed gastric emptying

The role of gastric emptying in GERD remains poorly understood. Delayed GE has been associated with GER disease,[52] nevertheless promotility agents do not reduce GER symptoms in adults. [53]

With regards to fundoplication, it seems fairly well established in adult patients that fundoplication increases gastric emptying rate.[54,55] The relation 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.[56,57] However, a large prospective trial, observed no relationship between gastric emptying and outcome of surgery.[54,58] 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 accelerated after surgery. However, since pre operative gastric emptying does not predict post operative outcome, authors suggest that gastric emptying is unnecessary in the work up for fundoplication.[59]

We measured gastric emptying in ten children before and after fundoplication and observed that the four patients who developed postoperative dysphagia had a longer gastric emptying half time compared to the patients that did not develop dysphagia. [31] 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. Therefore, some authors have made a case for more caution in the use of fundoplications.[9,10]

Medical therapy for GERD in children is not optimal and although new therapeutic approaches are are being investigated in adult patients, they will not be available in the near future. Therefore, fundoplication will remain an option of last resort in the treatment of severe, therapy resistant GERD 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 are currently widely used to diagnose esophageal motility disorders in adults, but it is still unclear whether Chicago metrics are able to predict post fundoplication dysphagia prior to surgery. Moreover, Chicago classification and normal HRM values are not available for children. New data suggests 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 and flow and derives a dysphagia risk index (DRI) which relates bolus movement and pressure generation within the esophageal lumen. This contrasts with the standard methods which analyses bolus movement and pressure generation separately.

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 and post surgery, since the relationship between delayed gastric emptying and complications after fundoplication is still not clarified.

Conclusion

Recent developments in the assessment of GER parameters, esophageal and gastric motility may enable us in the future to better predict the risk of post operative complications pre operatively. This development is essential for careful selection of pediatric patients for fundoplication due to refractory GERD.

Take home messages

- pHMII and conventional manometry is unable to predict postoperative dysphagia
- AIM analysis combines impedance and manometry values to derive an Dysphagia Risk Index
- The Dysphagia Risk Index seems to be able to predict postoperative 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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