Gastroesophageal reflux in children: the use of pH-impedance measurements and new insights in treatment
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Summary

GER is the passage of gastric contents into the esophagus and is referred to as GER disease (GERD) when GER causes troublesome symptoms and/or complications.\textsuperscript{1,2} GERD in infants and children is sometimes difficult to diagnose and even more difficult to treat. The diagnosis of GERD is hampered by the fact that GER symptoms such as irritability and crying, feed refusal and regurgitation are common problems in infants and these symptoms are not specific for GERD. Furthermore, diagnostic criteria for the objective diagnosis of GERD with commonly used diagnostic tests such as pH-metry, pH-impedance monitoring and endoscopy are poorly or not well defined.

Combined pH multichannel intraluminal impedance (pH-impedance) monitoring is a method to measure bolus flow in a lumen and was first used in infants in 1996.\textsuperscript{3} Because pH-impedance assesses bolus movement in the esophagus, GER can be detected independently of the acidity, allowing detection of non acid GER as well. Particularly in infants who drink milk or formula (potent buffers of stomach fluids),\textsuperscript{4} non acid GER plays an important role in terms of numbers of GER episodes and symptom association.\textsuperscript{5} PH-impedance is now recommended for the detection of GER rather than conventional pH-metry, by the European Society for Pediatric Gastroenterology Hepatology and Nutrition and the North American Society for Pediatric Gastroenterology Hepatology and Nutrition.\textsuperscript{2}

Not only the diagnosis of GERD is difficult, treatment of GERD in the pediatric population remains a major challenge as well. Proton pump inhibitors (PPIs) are most commonly prescribed and the use in infants has increased exponentially since the late nineties.\textsuperscript{6} PPIs have been shown to reduce acid secretion in infants and children\textsuperscript{7-10} and promote esophageal healing in patients with esophagitis.\textsuperscript{11,12} Although PPIs effectively reduce esophagitis a recently published systematic review shows that PPI treatment is not effective for the reduction of GER symptoms in infants.\textsuperscript{13} Efficacy data on the reduction of GER symptoms during PPI treatment in older children is less convincing. When children continue to experience severe symptoms and/or esophagitis despite treatment with high doses of PPI, anti-reflux surgery (fundoplication) may be a treatment of last resort. However, the indications for this surgical procedure are poorly defined in children\textsuperscript{2,14,15} and the effect of fundoplication on GER, esophageal motility and gastric emptying before and after surgery has not been prospectively studied in children.

Our group has an interest in left side positioning as a means to reduce GER in infants. It has been shown that left lateral positioning (LLP) reduces GER compared to right lateral positioning (RLP).\textsuperscript{16-18} However, it remains unknown if the reduction of GER in LLP reduces symptoms of GER as well and could be a treatment intervention. Furthermore, the underlying mechanism of the difference in GER in LLP and RLP has not been elucidated. Transient lower esophageal sphincter relaxation (TLESR) is the underlying mechanism allowing GER to occur and the number of TLESRs is augmented by several triggers of which
gastric distension is the most prominent one. However, the currently known mechanisms do not seem to provide an explanation for the difference in GER in LLP and RLP. This thesis consisted of three parts; in **PART I** studies to optimize GER detection using pH-impedance and new insights into the use of pH-impedance were described. **PART II** focused on treatment of GERD in infants with left side positioning and surgical treatment in older children. A study to further understand the underlying mechanism of the difference in left and right lateral positioning is presented in **Part III**.

### Part I – The value of pH-impedance in the diagnosis of GER disease

The pH-impedance technique is recognized to be superior to conventional pH-metry as it has the ability to detect liquid or gaseous bolus flow (swallowed or GER), regardless of the acidity of the bolus. pH-impedance has been shown to increase the yield of symptom association analysis compared to pH-monitoring in adults.\(^{19}\) This has, however, not been investigated in children and infants. In **Chapter 1** the additional value of detecting different types of GER (such as pH-only GER, liquid/mixed GER or gas GER) was described in terms of the most optimal association between the types of GER and symptoms. GER-symptom associations were calculated using (1) standard pH-metry (pH-only); (2) detection of liquid and mixed bolus GER (impedance only); (3) detection of all bolus GER (liquid, mixed AND gas bolus GER on impedance); (4) pH-impedance detection of all GER, including pH-only GER (pH and impedance). Impedance detection of all bolus GER yielded a significantly greater number of symptom-positive patients compared to standard pH-metry. Furthermore, a high proportion of patients with normal esophageal acid exposure, had a positive symptom association on pH-MII monitoring. From this study it was concluded that including all impedance-detected bolus GER and excluding pH-only GER for analysis, yields the most optimal GER-symptom associations in infants and children.

**Chapter 2, 3 and 4** focus on a new way of interpreting pH-impedance tracings. Until recently pH-impedance tracings were only analyzed for the presence of GER and the tracing between GER episodes was disregarded. However, recently it was reported that impedance baseline values, measured when the esophagus is at rest, may provide information about the esophageal mucosa.\(^{20}\) The impedance measurement uses electrical current to measure the conductivity of the adjacent lumen or the esophageal mucosa. When the lumen or mucosa is highly conductive, the impedance levels are lower. Therefore, impaired integrity of the esophageal mucosa with increased intra cellular spaces and highly conductive fluids in the esophagus possibly yields a lower impedance baseline (the impedance signal at rest).\(^{20}\) This new diagnostic paradigm may have potential in infants with GERD, who are difficult to endoscope safely and in whom antireflux medication is prescribed frequently without proof of mucosal changes. In **Chapter 2** we reanalyzed the impedance baseline values in infants before and after PPI treatment. This study was performed in 21 infants with symptoms of GER disease (mean age: 7.4 ± 4.2 weeks) before and after a week of PPI (esomeprazole) therapy. In infants with a low
baseline (<1250 Ohm) before therapy (n=15) the baseline increased significantly during treatment. In patients with normal baselines (n=6), no change in baseline was observed. In addition, patients with the lowest baseline before treatment had the greatest increase on PPI therapy. The data from this study suggest that low impedance baselines may be a new marker of esophageal mucosal integrity. This study was however uncontrolled and it remained unknown whether impedance baselines were associated with GER symptoms.

In Chapter 3 impedance recordings from 53 infants (0-6 months) enrolled in randomized placebo controlled trials of antacid and proton pump inhibitor (PPI) treatment were analyzed retrospectively in an automated fashion. Infants underwent 24hr pH-impedance monitoring prior to and after two weeks of double blind therapy with placebo, antacid, omeprazole (PPI) or esomeprazole (PPI). Baselines increased significantly on omeprazole and esomeprazole. Baselines in the placebo and antacid group did not change on therapy. The increase in baselines was most strongly driven by a reduction in acid GER episodes. We hypothesized that patients with low baselines before therapy would respond better to treatment. However, patients with a low baseline did not show a better symptomatic improvement on treatment. Therefore, despite encouraging results in terms of the increase in baseline on PPIs, the clinical impact of this observation remains to be defined as targeting therapy at infants with low baselines does not improve symptomatic response to treatment.

The assumption that baselines reflect on the status of the esophageal mucosa was based on research in animals and in adults but had never been tested in children. In Chapter 4 the association between endoscopy (macroscopy and histology) and new pH-impedance parameters (the SAP and impedance baselines) was assessed. In this chapter we showed that conventional pH-impedance parameters do not correlate with endoscopy, as has been shown by others. Furthermore it was observed that impedance baselines are indeed lower in patients with reflux esophagitis and in patients with a positive pH-impedance test (positive reflux index or SAP). These data suggest that pH-impedance may indeed be a marker of mucosal integrity in infants as well.

The analysis of pH-impedance recordings is based on pattern recognition, the investigator analyses a line or color plot and judges whether a specific pattern represents GER. Guidelines for the analysis of GER on a pH-impedance tracing have been developed and automated analysis is available in all software packages. However, most investigators prefer manual analysis to ensure confidence in the outcome. This introduces the potential for inter observer variability as investigators are usually self-trained in the analysis of GER on pH-impedance recordings. In Chapter 5 the inter and intra observer variability between international experts in the field of pH-impedance analysis and automated analysis and intra observer variability was assessed. Ten pediatric 24-hr pH-impedance tracings were analyzed by ten observers from seven world groups and with automated analysis. Detection of GER episodes was compared between the majority consensus (>6) of the observers and automated analysis. Overall, 42% of liquid and mixed GER events were scored by
the majority of observers. The numbers of GER detected per 24hr study by the observers ranged considerably from 4-19 in one study to 30-240 GER episodes in another study. Compared to majority consensus (≥6 observers) automated analysis has a 94% sensitivity rate and 74% specificity rate. Intra observer agreement was assessed in three observers and was moderate to excellent. Considering the poor inter observer outcomes automated analysis seems favorable over manual analysis due to its reproducibility. However, the relatively low specificity suggests the need for refinement of automated analysis before widespread use can be advocated.

**Part II – Treating GER disease in complicated patients**

In pediatric patients not responding to conservative treatment (feed thickening, lifestyle changes, smaller more frequent meals) and acid inhibitors, treatment options are limited. A recent systematic review showed that PPI treatment is not superior to placebo for the treatment of GER symptoms in infants.\(^\text{13}\) The ineffectiveness of PPIs may be explained by the fact that PPIs do not reduce the total number of GER, PPIs merely reduce acidity of GER, and weakly acid GER causes GER symptoms in infants as well.\(^\text{5,10}\) A therapy that does reduce the number of GER episodes has been much awaited. Left lateral position (LLP) may be a simple intervention providing such a treatment strategy as it has been shown to reduce GER in infants.\(^\text{16,17}\) It is unknown however, if LLP also has the potential to reduce GER symptoms and thus whether it can be a treatment strategy for GERD in infants.

In **Chapter 6** we performed a randomized sham procedure controlled trial to assess the effect of LLP in combination with anti-secretory therapy on GER and symptoms of GER in infants. Sixty-six infants (0-6 months) with symptoms suggestive of GER disease were investigated using pH-impedance and a gastric emptying breath test. Fifty-one infants demonstrating a positive relationship between GER and symptom episodes such as crying, coughing or regurgitation (symptom association probability>95%) were included. Infants were randomized to LLP or sham position (i.e. supine positioning, with the head of the bed elevated) in combination with PPI or sham medication, antacid therapy. Patients were therefore randomized to one of four treatment groups 1. PPI+ LLP, 2. PPI+ head elevation, 3. Antacid+ LLP or 4. Antacid+ head elevation. Position interventions were performed for 2 hours following feeding (infants were directly supervised to prevent accidental prone positioning and the risk of sudden infant death syndrome). After two weeks the studies were repeated on therapy. Compared to their respective sham therapies, LLP therapy reduced the number of impedance-detected GER episodes, and PPI therapy reduced acid GER. The combination of the two therapies was the most effective way of reducing all GER and vomiting was reduced. Despite a clear improvement in GER frequency and vomiting however, there was no concomitant reduction in symptoms of crying in this or any other treatment arm. Across the board, the change in GER did not correlate with a change in symptoms. However, interestingly, symptomatic improvement did appear to occur in
relation to a slower GE time. These findings raise the question whether GER symptoms which, whilst often considered to be due to GER are nevertheless non-specific, are the result of other causes. Furthermore, these results warrant future research into the role of gastric emptying in the genesis of GER and GER symptoms.

In children who continue to experience severe GER disease despite accurate acid suppressive therapy and conservative measures, anti-reflux surgery (fundoplication) may be considered. Large controlled trials assessing the efficacy in children and defining which children may benefit from fundoplication are lacking. In adults fundoplication has been shown to effectively reduce GER and the complications of GERD, however, fundoplication has also been shown to be equally effective to treatment with PPIs.\textsuperscript{23} Prospectively acquired data on GER and esophageal motility before and after surgery are lacking. In Chapter 7 the first study in infants describing GER, esophageal motility, gastric emptying and symptoms before and after fundoplication is presented. In this chapter we also introduce a highly novel and promising technique, automated impedance manometry (AIM), to predict the risk to develop the complication of post operative dysphagia. AIM analysis is an objective, reliable and reproducible tool that combines simultaneous impedance and manometry measurements to assess esophageal function. AIM analysis allows derivation of the dysphagia risk index from new AIM variables that better describe the interaction between bolus movement and pressure generation within the esophageal lumen. This contrasts with the standard methods which analyse bolus movement and pressure generation separately. In Chapter 7 combined impedance-manometry, 24hr pH-impedance and gastric emptying breath tests were performed in ten children (median age 6.4, range 1.1–17.1 years) before and after laparoscopic anterior partial fundoplication. The number of GER episodes reduced significantly after fundoplication. Esophageal peristaltic contractions remained unaltered although the percentage of complete lower esophageal sphincter relaxations was reduced after fundoplication. Four (40%) patients developed post-operative dysphagia. In those patients pre-operative gastric emptying was delayed and AIM analysis derived dysphagia risk index was significantly higher. Two patients had to undergo redo fundoplication due to recurrent symptoms. In this study it was shown that fundoplication in children reduced GER without altering esophageal motility. Nevertheless, complication rate was high. AIM analysis may be the first objective esophageal function parameter to allow detection of subtle esophageal abnormalities potentially leading to postoperative dysphagia.

Part III – Underlying mechanism of different GER profiles in right and left lateral position
It has been shown in previous work by our group\textsuperscript{16-18} and in this thesis that left side positioning reduces GER. However, the currently known mechanisms that control triggering of TLESRs do not seem to explain the reduction of GER in left side position. Therefore Chapter 8 describes the influence of LLP and RLP on GER in adult GERD patients and...
healthy adult controls and the underlying mechanisms (gastric emptying, gastric distension and gastric acid distribution). Ten GERD patients and ten healthy controls were included. All were studied for 90 minutes (30 minutes before infusion of a test meal, 30 minutes post-prandial in either RLP or LLP (randomly assigned) and then switched to the alternate position for 30 minutes). The study was repeated on a separate day in reverse position order. TLESRs, GER, gastric emptying rate and gastric distension were recorded during the study. In RLP GERD patients had an increased number of TLESRs and GER compared to LLP in the first postprandial hour whereas the number of TLESRs in healthy controls did not change in RLP compared to LLP. In GERD patients gastric emptying was more rapid and proximal gastric distension was more pronounced. The difference in numbers of TLESRs and GER in GERD patients in RLP and LLP may be explained by more rapid gastric emptying and more pronounced distension of the proximal stomach. It should be recognized that, whilst consistent with known physiological effects, our findings are inconsistent with clinical dogma that gastric emptying is delayed in GERD patients and, therefore, accelerating GE will lead to a reduction in GER. Our findings suggests that the interplay in different regulatory mechanisms in GERD patients may be different to healthy controls and that the triggering of TLESRs may be more complicated than currently understood.
Discussion and future perspectives

This thesis describes new insights into diagnosing and treating gastroesophageal reflux disease (GERD) in the pediatric population. In this final chapter, the findings of the thesis are discussed and future perspectives on the diagnosis and treatment of GERD in infants and children are provided.

Diagnostics

With the introduction of pH-impedance in the nineties, researchers were able to detect acid as well as non acid GER. In infants and children, who frequently experience non acid GER, pH-impedance was thought to resolve many issues in diagnosing GERD due to its ability to detect all types of GER. Indeed it has been shown that pH-impedance detects more GER than pH-metry. However it was unknown if symptoms in infants were related to non acid GER as well and if detection of all GER would improve symptom associations. In Chapter 1 it was confirmed that detection of all types of GER by pH-impedance is superior to acid only detection by pH-metry in term of detection of symptom associations.

It was hypothesized that a positive GER – symptom association based on pH-impedance would identify patients who would benefit from GER treatment. Chapter 6 is interesting from a diagnostic point of view as we observed that a positive symptom association based on pH-impedance did not select patients in whom symptoms diminished after a treatment strategy that reduced GER. Thus, although pH-impedance detects non acid GER as well, and is superior to pH-metry to detect associations between GER and symptoms, it does not identify patients that benefit from a GER reducing therapy. Currently, symptom association indices are based on research in adults and future research should focus on the development of a symptom association index for the pediatric population.

pH-impedance has also limitations. One limitation is the large difference in analysis between experts in the world (Chapter 4), and this difference is likely to be even greater amongst non experts in pediatric gastroenterology. The poor reproducibility compromises the use of impedance and the comparability of studies between different centers. Before we can move forward to increase diagnostic power of impedance, consensus needs to be reached on the detection of GER on impedance measurements. Furthermore, validated automated analysis should be developed to ensure reliable and reproducible assessment of pH-impedance tracings. A meeting to reach such a consensus is being organized and this hopefully will lead to the development of validated automated analysis.

For the inter observer study only one software system was used (MMS). Although the technical aspects of pH-impedance recordings are similar in all software packages, the analysis screen looks quite different. Furthermore automated analysis is based on entirely different algorithms that detect different GER episodes. Moreover, symptom association calculations are different between the different manufacturers. This undoubtedly leads to different outcomes which may in turn lead to a different diagnosis and treatment, merely
caused by the use of different software. This is unsatisfactory and to realize comparability between the systems, companies must start a dialogue to create software that provides similar outcomes.

Until recently, pH-impedance tracings were only analyzed for GER episodes. However, impedance baselines, the impedance signal while the esophagus is at rest, varies considerably between patients. It has been suggested in adult literature that impedance baselines may be a marker of mucosal integrity. In chapter two, three and four, this new way of interpreting pH-impedance tracings was investigated. Our data indeed suggest that impedance baselines may be a marker of GERD severity in infants. Although a relationship between symptom severity and baselines was not identified, these results are promising. Future research should assess if impedance is able to detect patients at risk for esophagitis. Impedance measurements are easier and safer to perform in infants than endoscopy and therefore has great potential in this patient population. Furthermore a better tool to identify patients who will respond to treatment is much awaited. Possibly new pH-impedance parameters combining conventional parameters (numbers of GER episodes and acid exposure) with new parameters (SAP and baselines) can contribute to this identification.

A highly novel method that allows objective, reliable and reproducible assessment of esophageal function is automated impedance manometry (AIM) analysis. AIM analysis combines in an automated fashion impedance (bolus movement) and manometry (pressure in the esophagus). Thus far, AIM has been used to identify aspiration and to identify the risk for development of post operative dysphagia. Preliminary data also shows that AIM analysis is able to objectify globus feeling. Although AIM analysis is more complex than standard methods, it is automated and simple to apply. This new analysis has great potential to unravel pathophysiological mechanisms in esophageal disorders.

Treatment
As discussed previously, the treatment options in infants and children with GERD are limited. Undoubtedly this is partially caused by the broad definition of GERD and the above mentioned drawbacks of diagnostic tests. Furthermore, the lack of efficacy of acid suppressive medication has been attributed to the inability to reduce the total number of GER. In Chapter 6 a study was presented in infants with a proven association between GERD and symptoms in whom a reduction in total numbers of GER and in acid exposure was achieved with left side positioning and PPI therapy. Despite the patient selection and the reduction of GER, the expected reduction in symptoms of irritability and crying did not occur. The questions that rise from this study are ‘Did GER cause the symptoms in the first place in these patients with a positive GER symptoms association?’ and ‘What diagnostic tools are needed to select patients with GERD that in fact will benefit from a therapy that reduces GER’.
Another question that rises is: ‘How to treat infant with GERD in the light of all these negative treatment studies?’ A pragmatic, symptom managing approach in combination with education about GERD may be the best current treatment. It is important to educate parents on normal GER patterns in infants. Physiologic al regurgitation occurs regularly in up to 70% of the 4 month old infants and usually resolves in the first year of life. Parents are often worried that GER may harm the esophagus. This is however unlikely in infants because GER is non acidic for a substantial part of the day. Furthermore, it is important to educate parents about normal infant crying behavior. In healthy infants crying lasts approximately two hours per day at two weeks of age, at six weeks of age the crying peaks at three hours per day, and gradually decreases to about one hour at three months. A crying infant is very distressing and parents may view the crying as an indictment of their care giving ability or as evidence of illness in their child. It is important to address these issues and to counsel parents regarding effective responses to crying. Extensive research regarding the coping with crying infants has been performed in colicky infants, an infant disease with an overlap with GERD. In a controlled trial in colicky infants parental counselling reduced crying from 2.6 to 0.8 hours per day. Although colic and GERD are different entities, families with infants with GERD may benefit from this pragmatic approach.

Another interesting area with an overlap with GERD is cow’s milk protein allergy because the symptoms of cow’s milk allergy and GERD (crying and irritability around feeds) are typical for both diseases. Some children with symptoms of GERD receive a trial of hypoallergenic formula and improve significantly, however the effect of hypoallergenic formula on GERD has not been tested. Future research may be able to identify the relation between GERD and cow’s milk allergy and the effect of hypoallergenic feeds on GER symptoms.

In older children the treatment of GERD is challenging particularly in children refractory to acid suppressive therapy. Some children may benefit from a TLESR inhibitor, such as Baclofen, although doctors and patients should be mindful of the possible side effects. When all treatment options have been exhausted and other causes of the complaints are excluded, surgery may be considered. When surgery is considered, the child and the parents should be made aware of the complications and realistic outcomes (Chapter 7). Some children may benefit from surgery however, we are currently unable to select those patients. Hopefully, the dysphagia risk index as assessed with AIM analysis, will be able to guide future patient selection for surgery. Large studies are required to confirm the value of AIM analysis and the dysphagia risk index.

(Patho)physiology

Previous studies have shown a difference in numbers of GER in left and right lateral position in infants. We were interested if this difference could be observed in adult
patients and healthy controls as well. Furthermore, the underlying mechanisms for the increase in GER in right lateral position had not been investigated. In Chapter 8 a study assessing esophageal motility, GER and gastric involvement was performed in GERD patients and healthy controls. All subjects were positioned in right and left lateral position. We observed no difference in GER in healthy controls, whether they are positioned the left or right side, whereas GERD patients had significantly more transient lower esophageal sphincter relaxations (TLESRs) and GER in the right lateral position. As possible underlying mechanisms greater distension of the proximal stomach and faster gastric emptying were observed when GERD patients were positioned on the right side. This leads to many questions that are as yet unanswered, such as 'what causes the distension of the proximal stomach in GERD patients?', 'Is this distension specific to GERD patients' and 'What is the role of faster gastric emptying in GERD?' The association between more rapid gastric emptying and more TLESRs and GER is consistent in right side position, but still unexplained. Furthermore, in Chapter 6 we observed that an increase in gastric emptying rate was associated with a decrease in symptoms. These findings are paradoxical and warrant further research into the exact role of gastric emptying in GERD.

Ultimately, by refining the definition, improving diagnostic tools to truly select GERD patients and continuing to investigate the underlying mechanisms we may in the future be able to define the similarities and differences between infants, children and adults with and without GERD.
Reference List


