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

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OUTLINE OF THE THESIS

Gastro-esophageal reflux (GER) is the passage of gastric contents into the esophagus and is a physiological phenomenon occurring in all infants and children.\(^8\) It is referred to as GERD when GER causes troublesome symptoms and/or complications such as but not limited to recurrent regurgitation, vomiting, heartburn, feed refusal, apnea, esophagitis and esophageal strictures.\(^7,8\) GERD is often diagnosed in infants in primary care setting based on symptoms without any diagnostic workup. However, GER symptoms such as irritability and crying, feed refusal and regurgitation are common entities in infants and these symptoms are not specific to and poorly correlate with GERD. This complicates the proper diagnosis of GERD.

Despite the increasing incidence of GERD and recent technical advances the objective diagnosis of GERD remains poorly defined. Commonly used diagnostic tests with diagnostic potential are pH-metry, pH-impedance monitoring and endoscopy, however the lack of normative data in children (due to ethical restrictions to introduce nasogastric catheters in healthy children) compromises the development of objective parameters. Not only the diagnosis of GERD is ambiguous, treatment in infants and older children not responding to commonly prescribed dietary, positional or medical interventions remains a major challenge. This thesis provides new insights into diagnosing and treating GERD and consists of three parts; in PART I studies are described to optimize GER detection and provide new insights into techniques to diagnose GER. PART II focuses on treatment of GERD in infants with left side positioning and surgical treatment in older children who are refractory to medical therapy. A study to further understand the pathophysiology of the influence of 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 and is now recommended instead of pH-metry by the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN).\(^8\) pH-impedance monitoring has the clear advantage that it is able to detect liquid or gaseous bolus flow, in combination with the ability to detect esophageal acid. However, the additional value of pH-impedance testing compared to pH-metry alone in children has not been defined. In Chapter 1 the additional value of detecting different types of GER (such as pH-only GER, liquid/mixed GER or gas GER) is described in terms of the most optimal association between the types of GER and symptoms. Chapter 2 and 3 focus on a new way of interpreting pH-impedance tracings. Until recently pH-impedance tracings were only analyzed for the presence of GER. However, more information seems to be available from the continuous 24 hr tracings. The pH-impedance measurement uses electrical current to measure the conductivity of the adjacent lumen or the adjacent esophageal mucosa when the esophagus is at rest.\(^122\) Impedance values measured through the mucosa are likely to represent the integrity of the esophageal mucosa, referred to as the impedance baseline. This new diagnostic paradigm
may have potential in infants, who are difficult to endoscope safely and are frequently prescribed proton-pump inhibitors without proof of mucosal changes. A better way is needed to diagnose GERD in infants and to target PPI therapy to the few infants who may benefit from this therapy. In Chapter 2 we reanalyze the impedance baseline values in infants before and after PPI treatment, to test the hypothesis that impedance baselines indeed reflect the status of the esophageal mucosal and improve when the mucosa is not exposed to gastric acid anymore. In Chapter 3 we analyze in an automated fashion the impedance baselines in infants who were enrolled in 2 randomized, placebo controlled trials. This study assesses the influence of PPIs, antacid and placebo on esophageal mucosa, as measured by the impedance baseline. Esophagitis is a complication of GERD and can be diagnosed with endoscopy. Recently international consensus was reached on the diagnosis of GER esophagitis in pediatrics. One of the challenges in the diagnosis of GERD in children is the lack of agreement between different diagnostic modalities. The agreement between pH-metry, pH-impedance and endoscopy, and symptoms of GER has been studied, however the results are ambiguous.92,102,103,218,219 One study compared pH-impedance with endoscopy and found no relationship in children with GERD.218 However, recently endoscopic findings of esophagitis have been correlated with low impedance baselines in adults suggesting a possible relation.122 In Chapter 4 the relation between endoscopy and pH-impedance is explored in terms of the correlation between endoscopic findings and mucosal integrity reflected by the impedance baseline value (Chapter 2 and 3) and conventional GER parameters such as number of GER and acid exposure. Since the introduction of pH-impedance measurement in 1991105 and the first study in children in 1996106, guidelines for the detection of GER on a pH-impedance tracing have been developed.75 Most investigators are self-trained in the analysis and consistency between observers of different groups around the world is unknown. Automated analysis is available in all software packages, however most investigators prefer manual analysis, introducing the potential for inter observer variability. In Chapter 5 the inter and intra observer variability between ten national and international experts in the field of pH-impedance analysis and automated analysis is assessed.

Part II – Treating GER disease in complicated patients

In patients not responding to conservative treatment (feed thickening, lifestyle changes, smaller and more frequent meals) and acid inhibitors, the treatment options are limited. A systematic review recently showed that PPI treatment is not superior to placebo for symptoms suggestive of GERD in infants,86 leaving the clinician with a great challenge to manage infants with GER. Our group has recently shown that GER in infants is significantly reduced in left lateral position.49,50 It is unknown however, if left lateral positioning also reduces symptoms of GERD and whether it can be a treatment option. In Chapter 6 we present a randomized sham procedure controlled trial to assess the effect of left
lateral position in combination with anti-secretory therapy on GER and symptoms of GER in infants 0-6 months of age. When children continue to experience severe GERD despite accurate acid suppressive therapy, surgical fundoplication is regarded as a treatment option of last resort. However, large controlled trials assessing the efficacy in children and to define which children may benefit from fundoplication are lacking. In adults fundoplication has been shown to be effective in reducing GER and the complication of GERD, however, fundoplication is equally effective to treatment with PPIs. Furthermore, prevalence of complication (such as GERD recurrence and dysphagia) is high in children, especially in neurologically impaired children. Chapter 7 comprises the first study in infants describing GER, esophageal motility, gastric emptying and symptoms before and after fundoplication. In this chapter we use a highly novel and promising technique to predict the risk to develop the complication of post operative dysphagia.

**Part III – Underlying mechanism of different GER profiles in right and left lateral position**

Our research group has a special interest in the influence of side position of GER as it is a non-pharmacological, effective way to reduce GER. Although left side positioning clearly reduces GER, the currently known mechanisms that control triggering of GER do not seem to explain the reduction of GER in left side position. Therefore Chapter 8 describes the influence of left and right lateral position on GER in healthy adult volunteers and adult GERD patients and the underlying mechanisms (gastric emptying, gastric distension and gastric acid distribution).

This thesis concludes with a summary, discussion and future perspectives (in English and in Dutch) based on the presented studies.
Reference List


