Pediatric gastroesophageal reflux and upper gastrointestinal tract motility: the use of multichannel intraluminal impedance and high resolution manometry
van Wijk, M.P.

Citation for published version (APA):
van Wijk, M. P. (2010). Pediatric gastroesophageal reflux and upper gastrointestinal tract motility: the use of multichannel intraluminal impedance and high resolution manometry

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Summary and general discussion

Parts of the general discussion have been published as:


SUMMARY

Gastro-esophageal reflux disease and other motility disorders of the upper gastrointestinal tract are common in infancy and childhood and are frequently difficult to treat. To come to better treatment regimes for these children, more insights are needed with respect to both physiological and pathophysiological mechanisms. In the last decade, novel and better techniques have been developed, such as multichannel intraluminal impedance (MII) and high resolution manometry (HRM) to study upper gastrointestinal motility. Multichannel intraluminal impedance (MII) is a technique which enables the detection of flow of liquids and/or gas through the gastrointestinal lumen. Because MII detects esophageal flow directly, it is possible to detect all GER episodes and in combination with a pH sensor classify these into acidic, weakly acidic, and weakly alkaline GER. Due to the multiple measuring sites, the direction of flow can be determined. Hence, GER can easily be discerned from swallowed material, making dietary restrictions unnecessary. Furthermore, this makes it possible to study the mechanisms of bolus and acid clearance and provides information on the proximal extent of a GER episode, which can be helpful for determining a relation between GER and extra-esophageal symptoms.

High resolution manometry (HRM), records pressure throughout the gut with a large number closely spaced (1cm or less) pressure sensors between which pressures can reliably be interpolated. These data can then be shown as a continuum of pressures using pressure topography (iso-contour) plots (see figure 4 of the introduction). Furthermore, information on sphincter (upper esophageal sphincter (UES) and lower esophageal sphincter (LES)) relaxation relative to the esophageal motor pattern can easily be gathered, while UES pressure is not recorded during conventional manometry.

In this thesis, studies are presented that further optimize the analysis of MII. Furthermore, these techniques were used for physiological and pathophysiological studies in infants and adults, aiming to shed more light on the development of swallowing and the mechanisms involved in the pathophysiology of gastroesophageal reflux (GER) disease. Finally, a study is presented which aimed to give a detailed description of the gastroesophageal function in infants and adults that were born with esophageal atresia.

PART I - OPTIMIZATION OF THE MULTICHANNEL INTRALUMINAL IMPEDANCE TECHNIQUE

Although MII was developed for the recording of intra-esophageal flow almost 20 years ago, most studies using this technique were only published in recent years. Criteria for the analysis of liquid boluses were developed and validated earlier, but the data on the exact features of MII tracings with respect to the detection of gas GER episodes in humans was lacking. In Chapter 1 a study is presented in which MII patterns of known gas GER episodes were characterized and more insight is gained on the interrelationships
between the magnitude of impedance change, luminal diameter and presence of electrode-mucosa contact. To do this, ten healthy adult volunteers were intubated with a combined MII-manometry catheter, after which they were asked to drink 600mL of carbonated drink (Coke) twice. The resulting belches (gas GER episodes) were analyzed in detail and novel criteria for the detection of gas GER were presented as previously used criteria proved poorly sensitive. An additional group of 5 volunteers underwent combined MII-videofluoroscopy. This revealed a close relationship between the luminal diameter and the magnitude of impedance change, as well as between the presence of electrode-mucosal contacts. It is impossible to take these factors into account when analyzing MII studies in general, but the fact that they may have a major impact on impedance levels should be kept in mind when interpreting the results.

As MII detects all GER episodes, it theoretically offers the opportunity to find a relationship between non specific symptoms (such as irritability or crying) and GER episodes in an individual patient. To do so several statistical methods were previously developed, with symptom association probability (SAP) score being the one with least drawbacks. However, this score was developed in adults with specific GER disease symptoms, such as heartburn. The SAP is highly dependent on a number of test characteristics, such as the time interval used during which both symptom and GER episode should occur to define them as being related. Furthermore, a minimal number of symptoms can be set, below which SAP has little value. In Chapter 2 we set out to optimize SAP criteria for its use in infants. We studied 10 symptomatic infants with MII for 48 hours, during which period symptoms were marked. MII recordings were analyzed for the occurrence of bolus reflux episodes and SAP was separately calculated for Day 1 and Day 2. Assuming that SAP should agree over the two days when the right test characteristics were used, the two SAPs were analyzed for their agreement using different test characteristics. Optimal time windows and minimal numbers of symptoms needed are presented for cough, crying and regurgitation.

PART II - PHYSIOLOGICAL STUDIES

Early enteral feeding in premature infants, particularly with expressed breast milk, assists in the development and normalisation of gut function and significantly reduces morbidities such as necrotising enterocolitis and sepsis. Oral feeding capacity is poor in the very preterm infant due to inadequate suck-swallow-breath coordination and leads to suboptimal nutrition and growth. With overall survival rates in these infants increasing, dysphagia is becoming a major clinical problem prolonging hospitalisation and increasing health care costs. Pharyngeal motility patterns involved in the development of swallowing are only partly understood. In Chapter 3 a detailed analysis of pharyngeal and upper esophageal sphincter (UES) motility in 18 premature infants is presented. Using HRM, these infants (corrected age at study: 31-37 weeks) were studied weekly for up to four weeks to show developmental patterns over time. In infants under the corrected age of 34 weeks,
there is an immaturity of the timing of pharyngeal contractions and UES relaxation. This observation is in concert with the clinical observation that infants of that age are only beginning to feed orally. Previously in infants with feeding problems, attention was solely on the infant’s ability to swallow, while this study shifts focus to pharyngeal motility patterns that are clearly immature. The methodologies and findings described may provide a means to differentiate between poor feeding due to physiological immaturity of the pharynx and poor feeding due to other pathology.

The physiology underlying GER and the pathophysiology underlying GER disease was the focus for Chapters 4, 5 and 6. From a previous study it had become clear that when infants are placed in left lateral position, the number of GER episodes decrease, while gastric emptying (GE) slows down. In Chapter 4 a positioning regime was developed in which less GER episodes in the late post prandial period (when GER episodes become acidic) were achieved without slowing down GE. Ten healthy preterm infants were monitored with combined esophageal impedance-manometry. Infants were positioned in the left lateral position (LLP) or right lateral position (RLP) and then gavage-fed. After 1 hour, the position was changed to the opposite side. Subsequently, all infants were restudied with the order of positioning reversed. More transient LES relaxations and liquid GER episodes were found in RLP compared to LLP. In the RLP-first protocol, the number of transient LES relaxation and liquid GER episodes per hour decreased significantly after position change. GE was faster in the RLP-first protocol than in the LLP-first protocol. Results from this study were not easily explained by existing knowledge about neurophysiology and suggested the presence of subtle regulating mechanisms influencing the triggering of transient LES relaxations and GER episodes.

In Chapter 5 one such mechanism is investigated by looking at the threshold amount of constantly infused feed needed to trigger transient LES relaxation in the RLP and LLP. Eight healthy infants were studied using an esophageal impedance-manometry catheter incorporating an intra-gastric infusion port. After tube placement, infants were randomly positioned in RLP or LLP. They were then tube-fed their normal feed at a constant infusion rate of 160 mL/h. Recordings were made during the feed and 15 minutes thereafter. The study was repeated with the infant in the opposite position. During this study, more transient LES relaxations were triggered in the RLP compared with LLP. The percentage of feed infused at time of first transient LES relaxation was significantly lower in RLP compared with LLP. The volumes infused in RLP at the triggering of the first transient LES relaxation were so low that they were unlikely to induce gastric distension and thus suggest the presence of other mechanisms affecting the vago-vagal pathway leading to the occurrence of a transient LES relaxation. These mechanisms may involve sensing at the level of the esophago-gastric junction (EGJ) in addition to sensing of tension within the gastric smooth muscle.

Chapter 6 focuses on another possible neuroregulatory mechanism. It was already known that patients with gastroesophageal reflux disease show an increase in EGJ distensibility
and in frequency of transient LES relaxations induced by gastric distension, but a mechanism where distension of the EGJ itself influences the number of transient LES relaxations triggered was not yet considered. The effect of localized EGJ distension on triggering of transient LES relaxation in 10 healthy volunteers is described in this chapter. For this purpose an esophageal manometric catheter incorporating an 8 cm internal balloon adjacent to a sleeve sensor was developed to enable continuous recording of LES pressure during distension of the EGJ. Inflation of the balloon doubled the cross-section of the trans-sphincteric portion of the catheter. After catheter placement and a 30 minute adaptation period, the EGJ was randomly distended or not, followed by a 45 minute baseline recording. The healthy subjects consumed a ‘refluxogenic meal’ and recordings were made for 3 hours post prandially. A repeat study was performed on another day with EGJ distension status reversed.

The number of transient LES relaxation increased during periods of EGJ distension with the effect being greater after a meal. From this observation it was concluded that EGJ distension augments meal-induced triggering of transient LES relaxation in healthy volunteers. It is unlikely that a ‘classic’ gastric mechanoreceptor mediated mechanism can explain this for two reasons. One, no accommodation of the effect was seen during prolonged distension. Second, MRI imaging of the catheter shows the diameter of the proximal stomach largely exceeding the intra-gastric part of the sleeve/balloon. These data suggest the existence of a population of vagal afferents located at sites in/around the EGJ that may influence triggering of transient LES relaxation.

PART III - COMPLEX FORMS OF ESOPHAGEAL MOTILITY DISORDERS

In Chapter 7 the gastroesophageal function of esophageal atresia (EA) patients is described. A combined multichannel intraluminal impedance, manometry and gastric emptying test was performed in 10 infants and 10 adults. The analysis focused on mechanisms underlying GER episodes as well as gastroesophageal function in terms of motility patterns and resulting bolus clearance. It was shown that transient LES relaxation is the main mechanism underlying GER events in patients with EA. Most infants and adults have impaired motility, delayed bolus clearance and delayed gastric emptying. However, normal motility patterns were seen in a minority of patients. Normal clearance was seen in about 40% of all swallows, while only 21.2% was accompanied by a normal motility pattern.
GENERAL DISCUSSION

In this thesis, two novel techniques are used to describe physiological and pathophysiological mechanisms of pediatric gastrointestinal motility disorders, such as gastroesophageal reflux (GER) disease.

HRM has now been used extensively in adult pharyngeal and esophageal studies and has proven its clinical benefit especially in achalasia. However, it is hampered in children and especially infants, because the diameter of both water perfused and solid state HRM catheters increases with the number of channels needed. Additionally, the stiffness of the catheter increases with the number of pressure sensors in solid state catheters, making intubation less tolerable. As a result, standard HRM catheters are only beginning to become commercially available for use in infants and children. Very recently a standard protocol was developed for HRM studies in the pediatric age range. Novel developments using optical fibre techniques are ongoing and may result in HRM catheters with diameters suitable for studies in (premature) infants with a large number of pressure points. Of course, such catheters will primarily be a research tool. However, they might well prove to have a clinical role in e.g. infant dysphagia or for pre-operative testing in those children undergoing fundoplication for GER disease.

With the introduction of MII, most disadvantages of classical pH monitoring seem to have been overcome and using MII, it was shown that conventional 24-hour pH-monitoring only detects a minority of GER episodes. With an increasing body of evidence showing a role for weakly acidic bolus GER and gas GER in symptom generation, the measurement of acidity alone provides an incomplete picture of the degree of bolus reflux and the relationship of bolus reflux to symptom episodes.

MII has its limitations, too. First, normal values do not exist in the pediatric age range and although efforts to establish these have been made and are ongoing, it is unlikely that truly normative data will ever become available because of ethical considerations preventing the study of healthy children with invasive techniques. By adding a pH sensor to the MII catheter both acid and weakly acidic GER can be detected.

Combined MII-pH catheters are now commercially available for use in infants and children. Other issues limiting its clinical use at present are the costs of consumables, which are 4 to 5 times higher than a pH study, and the time required for analysis, which ranges from 30 minutes to 4 hours depending on the frequency of reflux, impedance baseline levels and the experience of the analyst. The recent development of displaying impedance patterns in spatio-temporal colour-plots, enhances easier recognition of GER and will probably improve sensitivity of GER detection and reduce analysis time. MII is most useful in clinical settings when children present with non specific symptoms which could be related to GER disease.

In this thesis the detection of gas GER episodes was optimized by analysing known gas GER episodes in detail, resulting in newly developed criteria. However, rather than making
automated detection easier, our data show that impedance values are dependent on factors such as intraluminal diameter and electrode-mucosa contact that cannot easily be incorporated in analysis software. Further studies are clearly needed to optimize automated detection of gas and liquid GER. One approach could be to step away from general criteria which are applied to all patients and move towards a more personal calibration of impedance values based on each study itself.

Another difficult issue in MII testing in infants and children is how to discriminate a normal physiological from a pathological study. Normal values do not exist and it is ethically unlikely that they will ever become available. A clear temporal association between GER episodes and symptoms seems to provide convincing evidence of one causing the other. However, several difficulties arise. First, not all patients experience symptoms during a 24-hour study period. Second, a clear definition of temporal association is lacking. In this thesis, we have defined the minimal number of symptoms and the optimal time interval for defining a relation between symptoms and GER episodes. This will result in better recognition of GER related symptoms, however our technique is not ideal. In future prospective intervention studies are needed to objectify the value of several means of symptom-GER association. Such studies should look for associations before and after treatment and use different epochs to answer the question: which of these measures most closely reflects reality. It may well be that such studies will show, as we did for infants with crying, that different cut-off values or epochs are appropriate for different symptoms or age groups. It could also show that none of these estimates of association are good enough and novel statistical means need to be developed.

Despite these issues with respect to MII analyses, the test can provide insights into (patho)physiology, especially when combined with (high resolution) manometry. Scientific studies in infants and children are only ethically acceptable when a child is intubated for (other) clinical reasons. This limits the amount of research that can be done in these age groups. One exception, controversial as it may seem, are premature infants. A large group of premature infants is healthy (i.e. no signs/symptoms of GER disease) apart from the inability to feed orally. Most of these infants are fed through nasogastric tubes. If MII-manometry catheters are used that incorporate a gastric infusion channel, these infants can be studied during and after their feeds, although there are a number of limitations. As mentioned above HRM can only be performed with a perfused catheter and limited number of sideholes. Solid state catheters are no option because they lack a gastric infusion port. Furthermore, the volume of the water perfused needs to be small, because it should not interfere with the infant’s normal daily intake. Response times (time between the actual pressure change and the subsequent change on the tracing) are therefore slower.

Nevertheless, for this thesis water perfused HRM was used to study the development of swallowing in premature infants 31-38 weeks corrected age. The results not only give insight in the normal developmental physiology, but could also serve as a reference for
infants who are being investigated for feeding difficulties. Future studies are needed to elucidate whether HRM testing of pharyngeal and upper esophageal sphincter motility would be of clinical value in these infants.

Other studies in healthy infants comprised the role of posture in triggering GER events. We developed a positioning regime which reduces the number of GER episodes in the late post prandial period, when GER is known to become acidic, without delaying gastric emptying. Such a regime has the potential to become a first line treatment in infants with GER disease. However, it should be tested against and in combination with medication currently available. Recent data show that conservative measures are effective in many infants, but also that the effect of proton pump inhibitors in those infants not responding to conservative measures is very limited. In this light, it might well be that (optimized) posture regimes will prove more effective as a first line therapy than any pharmacological agent currently available.

Both posture studies presented as well as the study looking at distension of the esophagogastric junction, raise questions as to the neuroregulatory mechanisms involved in triggering transient LES relaxations. Although gastric distension is without dispute the main trigger of transient LES relaxations, it seems that more neuroregulatory mechanisms play a role. Both posture studies suggest a role for some form of intragastric sensing. However, the results are not in line with what would be expected on a physiological basis. If, for example chemoreceptors would be present in the proximal stomach, one would expect them to block transient LES relaxations when nutrients would be surrounding the EGJ and allow transient LES relaxations when no nutrients are present. Such a mechanism would prevent liquid GER to occur and allow for the venting of excess gas. In our study however, we saw more triggering of transient LES relaxations at lower volumes of infused feed in the right lateral position, when feed is pooling around the EGJ. It is clear that more research is needed to elucidate contributing factors, such as the nutrients involved, duodenal feedback mechanisms and perhaps immaturity of protective mechanisms in these premature infants. Alternatively this mechanism may allow for physiological reflux as a means to partially empty the stomach when an infant has been overfed. In our experimental paradigm we created a circumstance leading to pooling of fluid at the EGJ which could be considered highly un-physiological. The fact that infants are nursed supine is a convention of modern human civilization, whilst in more primitive cultures, an infant is typically nursed upright. There is no doubt that ‘SIDS safe’ body positioning and modern day nursing and feeding practices to which the human EGJ has not had the opportunity to evolve, contribute to the increasing incidence of problematic GER in infants. Further studies that may assist in understanding could include positional studies in patients with GER disease and in healthy adults; in order to establish that our observations can be replicated in an older age group with a mature anatomical configuration.

This is similarly true for the results found in the study looking at the role of EGJ distension on triggering of transient LES relaxations. Although the study is in line with
observations by many others and a potential neurophysiological substrate (vagal afferent neurons, projecting to the nodose ganglion which is known to be involved in triggering transient LES relaxation) was found in the crura of the diaphragm recently, it is still unclear why such a mechanism would exist. Nevertheless, our findings suggest it would be worthwhile to perform similar experiments in adults with GER disease, but also to perform neurophysiological experiments in animal models such as the ferret, which is well known for its similarities to human neurophysiology in terms of triggering transient LES relaxations.

In esophageal atresia patients, symptoms of GER disease and other upper gastrointestinal complaints are common. In this thesis we give a detailed description of gastro-esophageal function, both in infants shortly after their reconstructive surgery as well as in adults. The study shows that differences in gastroesophageal function abnormalities in infants and adults are subtle. More studies are needed to unravel the relation between these findings and endoscopic findings and incorporating both, to find the best follow up strategy for these patients.

In this thesis, a novel technique, multichannel intraluminal impedance, was further optimized for its use in infants and children. It was shown that with this technique and high resolution manometry, novel insights can be gained in the developmental physiology of swallowing and pathophysiology of GER disease, where this thesis focused on previously unconsidered neuroregulatory mechanisms. Meanwhile, these studies provide a basis for a potentially better treatment with less side effects than the pharmacological treatment that is often considered standard practice. Finally, the gastroesophageal function of patients with esophageal atresia is presented as just one example of many complex motility disorders. The techniques and results presented in this thesis will, without a doubt, lead to more fascinating research in all these areas, hopefully resulting in better treatment of children with very common motility disorders, such as GER disease.
REFERENCES


