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.
Small volumes of feed can trigger transient lower esophageal sphincter relaxation and gastroesophageal reflux in the right lateral position in infants

Michiel van Wijk
Marc Benninga
Geoffrey Davidson
Ross Haslam
Taher Omari

**ABSTRACT**

Gastric distension causes transient lower esophageal sphincter relaxation (TLESR) and gastroesophageal reflux (GER). We hypothesized that additional neuroregulatory mechanism play a role in triggering TLESRs.

**Objective:** Investigate the threshold amount of constantly infused feed needed to trigger TLESRs in the right lateral position (RLP) and left lateral position (LLP).

**Study design:** Eight healthy infants (3 male, GA: 32.9±2.4wks, corrected age: 36.1±1.3wks) 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 (62.5 (40-75) ml) at an infusion rate of 160ml/hr. Recordings were made during the feed and 15min thereafter. The study was repeated with the infant in the opposite position.

**Results:** More TLESRs were triggered in the RLP compared to LLP (4.0 (3.0-6.0) vs. 2.5 (1.0-3.0), p=0.027). First TLESR occurred at a significantly lower infused volume in RLP compared to LLP (10.6±9.4 vs. 21.0±4.9 ml, p=0.006). The percentage of feed infused at time of first TLESR was significantly lower in RLP compared to LLP (17.6±15.5 vs. 35.4±8.02%, p=0.005).

**Conclusion:** In the RLP, TLESRs and GER are triggered at volumes unlikely to induce gastric distension.
INTRODUCTION

Gastroesophageal reflux (GER) is very common during infancy.\(^1\) Most symptoms, such as regurgitation, resolve with age and are therefore no reason for concern. However, in infants with GER disease, GER can cause more severe symptoms, such as excessive crying, feed refusal, sleep disturbances and failure to thrive.

The esophagogastric junction (EGJ) anti-reflux barrier comprises lower esophageal sphincter (LES) and the crural diaphragm. During swallowing, these muscles relax simultaneously and allow the swallowed bolus to be transported into the stomach. Relaxation of the LES and crura also occurs without a preceding swallow. Such an event is called a transient lower esophageal sphincter relaxation (TLESR). TLESRs serve as a mechanism to vent gas from the stomach, but have also been shown to be the main mechanism underlying GER episodes in infants with occasional uncomplicated GER and those with GER disease.\(^2,3\)

Current data indicate that TLESRs can be triggered by gastric distension, e.g. following a meal.\(^4\) TLESRs are mediated via a vago-vagal pathway initiated by tension receptors located in the proximal stomach musculature.\(^5\) The vagal tension receptors have central terminals in the brain stem (nucleus tractus solitarius) which synapse with neurons of a central program generator that ultimately project to the LES and crural part of the diaphragm via vagal efferents, leading to a simultaneous relaxation of the LES smooth muscle and striated muscle of the crura.\(^6\) Cholecystokinin (CCK) receptors play a role in this pathway.\(^7-9\)

CCK is released upon food entering the duodenum and enhances triggering of TLESRs.7 The mechanism behind this has been postulated to be related to the CCK mediated fundic accommodation or direct enhancement of the vagal afferent response to gastric distension by CCK.\(^10,11\) Compared to healthy subjects, TLESRs do not occur more often in subjects with GER disease, not in infants, nor in adults.\(^3,9,12\) However, GER episodes during TLESRs are more often liquid and acidic in patients with GER disease.\(^3,9,12-14\) The mechanisms behind this selectivity remain largely unknown. It has been suggested that a so called ‘acid pocket’ in the proximal stomach in adults extends more proximally in patients with GER disease compared to healthy volunteers.\(^15,16\) Furthermore, enhanced acid secretion might play a role\(^17\) as well as factors such as enhanced or prolonged fundic accommodation and delayed gastric emptying of the proximal stomach.\(^18,19\)

In adults, right side body positioning compared to the left has been shown to exacerbate the number of TLESRs triggered post prandially as well as the number of acid GER episodes associated with it.\(^20\) In healthy infants, we have shown the same effect of right side positioning on TLESRs and liquid GER episodes and also demonstrated that gastric emptying was paradoxically faster.\(^21\) Furthermore, we have shown, that when the position of an infant is changed from left to right lateral one hour after a feed, the number of TLESRs and the number of liquid GER episodes increased in concert with the position change.\(^22\) This dramatic increase in TLESR/GER, occurring well after the completion of
a feed, under conditions of constant or possibly reduced intragastric pressure (due to reduced compression by abdominal organs such as the liver\textsuperscript{23} cannot easily explained by the classical TLESR pathway.

As currently described, TLESRs are triggered by gastric (primarily cardia) distension and mediated via a vago-vagal pathway initiated by tension receptors located in the proximal stomach musculature.\textsuperscript{4-6} Alternatively, the existence of (an) additional mechanism(s) which may modulate the TLESR vago-vagal pathway in relation to the presence of luminal contents in this region is yet to be explored. In this study, we hypothesized that amounts of liquid (feed) that produce minimal or no distension of the stomach would be able to trigger TLESRs in the right lateral position, but not the left.

**METHODS**

**Subjects**

We studied preterm infants who did not experience any symptoms related to GER disease or other gastro-intestinal diseases and were healthy apart from their prematurity. All subjects were studied at the Women’s and Children’s Hospital in Adelaide, Australia. For ethical reasons, all infants had to receive at least one of their daily feeds by gavage. The parents or legal guardians gave written informed consent before the commencement of each study and the protocol was approved by the Research Ethics Committee of the Women’s and Children’s Hospital, Children Youth and Women’s Health Services.

**Experimental protocol**

Each infant was studied on two occasions and subjected to two positioning protocols in a randomized cross over fashion (\textit{figure 1}). The assembly was manometrically positioned with its tip just distal to the lower border of the esophagogastric high pressure zone. The infants were then randomly positioned in either the right lateral position (RLP) or left lateral position (LLP) and gavage fed their normal feed (expressed breast milk or formula in the same volume normally used). During the second study, infants were positioned opposite to the first study. Feed volume and consistency were kept identical for both studies and the feed was infused at a constant rate of 160 ml/hr using two syringe pumps (1235 N, Atom Medical International, Japan). Manometry / impedance recordings started at the start of the feed infusion. After the feed, all subjects were studied for another 15 minutes.

**Esophageal impedance and manometry**

A purpose built combined multichannel intraluminal impedance and manometry catheter (outer diameter: 2 mm) that also allowed for gavage feeding was used (\textit{figure 2}). The assembly consisted of a water perfused manometric sleeve catheter with side holes at 3,
4.5, 6 and 11.5 cm proximal to the midpoint of the sleeve for recordings in the esophagus and pharynx. The incorporated sleeve had a length of 3 cm to allow for continuous measurement of LES pressure during breathing and swallowing associated movements of the LES relative to the assembly. Electrode rings positioned at 2.25, 3.75, 5.25, 6.75, 8.25 and 9.75 cm proximal to the midpoint of the sleeve allowed for the recording of 5 segments of intraluminal impedance throughout the esophagus. A feeding lumen was incorporated with its opening at the distal end of the assembly.

The esophageal side holes and the sleeve were perfused with degassed distilled water by a low-compliance pneumohydraulic perfusion pump (Dentsleeve; Wayville, South Australia, Australia) at 0.027 ml/min per channel. The pharyngeal side hole was perfused with air at a rate of 2.6 ml/min using the same pump. Pressure and impedance signals were acquired with a frequency of 50 Hz using a computerized acquisition system (Sandhill Scientific, Denver, Colorado).

**Figure 1 Study protocol.** Infants were randomly positioned in either the right lateral position or left lateral position. Each infant was studied a second time in the opposite position according to the same protocol. Infants received their normal feed, which was kept identical during the 2 studies and was infused at a speed of 160 ml/hour.

Small volumes of feed can trigger reflux in right lateral position.
Data analysis
All data were de-identified before analysis and analyzed with the investigator blinded from the protocol followed. Impedance tracings were analyzed for liquid, gas and mixed reflux episodes using established criteria.24,25 Manometry tracings were separately analyzed for TLESRs using criteria set by Holloway et al.26 Timing of TLESRs and GER episodes as well as the number of these events were compared between the RLP and LLP.

Statistical analysis
Normally distributed data are presented as mean ± SD and are compared between the protocols or between sides using the paired t-test. Proportional data were compared using Chi-square tests. Non parametric data and data where no assumption about the distribution was made are presented as median (range) and are compared with the Wilcoxon’s matched pairs signed ranks test. Parameters directly derived from time that were normally distributed and uncensored (percentage of feed infused at the time of first TLESR and volume infused at the time of first TLESR) are compared between positions using the paired T-test. However, censored parameters (percentage of feed infused at the time of first liquid GER episode and volume infused at the time of first liquid GER episodes) were compared between the RLP and LLP using Log Rank (Mantel-Cox) statistics. A p-value of less than 0.05 was considered statistically significant.

RESULTS
Subjects
Eight healthy infants (3 male, gestational age: 32.9 ± 2.4 wks, corrected age: 36.1 ± 1.3 wks) were studied. Mean weight at birth was 2064 ± 507 g and 2436 ± 276 g at the time of the first study.

Feeding volumes and time
Feed volume given to the infants was identical on both study days (62.5 (40-75) ml), and thus infused over an identical period of (23.4 (15.0-28.1) minutes). Five subjects received formula (Nan 1, Nestlé, Australia); 3 were fed expressed breast milk.

TLESRs and GER episodes
In one subject, the impedance catheter malfunctioned. For this patient, only manometry data were analyzed.
In the RLP, significantly more TLESRs and liquid GER episodes were seen during the entire study period (4.0(3.0-6.0) vs. 2.5(1.0-5.0), \(p=0.027\) and 4.0(2.0-7.0) vs. 1.0(0.0-5.0), \(p=0.043\) respectively, figure 3) as well as during the meal period alone (2.5(2.0-6.0) vs. 1.5(0.0-3.0), \(p=0.024\) and 2.0(2.0-5.0) vs. 1.0(0.0-3.0), \(p=0.041\) respectively, figure 3). The percentage of TLESRs associated with GER episodes was greater in the RLP compared to LLP (68.6% vs. 52.6% respectively, \(p=0.376\) for all GER and 65.7% vs. 36.8% respectively, \(p=0.051\) for liquid GER only).

During the study, the first TLESR occurred significantly earlier in RLP compared to the LLP (4.0 ± 3.5 min vs. 7.9 ± 1.8 min, \(p=0.006\)). Consequently, the volume of feed infused at the time of the first TLESR was significantly lower in the RLP compared to the LLP (10.6 ± 9.4 ml vs. 21.0 ± 4.9, \(p=0.006\)). This was also true for the percentage of feed infused at the time of occurrence of the first TLESR (17.6 ± 15.5% vs. 35.4 ± 8.02%, \(p=0.005\) (figure 4)).

The first liquid GER episode occurred at a lower infused volume in the RLP (estimated mean: 29.1 ml (95% CI: 17.3-41.0 ml)) compared to the LLP (estimated mean: 53.9 ml (95% CI: 34.5-73.4 ml), \(p=0.032\)), as well as at a lower percentage of feed infused (estimated mean: 45.5% (95% CI: 30.5-60.4%) vs. 78.8% (95% CI: 57.9-99.7%), \(p=0.016\)). The 25th -75th percentile for the volume (percentage of feed) needed to trigger the first TLESR was

---

**Figure 3 Number of TLESRs during the entire study (left) and meal period only (right).** Significantly less TLESRs were seen in the left lateral position (LLP) compared to the right lateral position (RLP), both during the meal alone as well as during the entire study. * \(p<0.05\), Wilcoxon’s matched pairs signed ranks test.
19.6 – 25.1 ml (30.1 – 44.0%) in the LLP. This range is much more variable in the RLP (1.7 – 21.5 ml (2.8 – 34.7%), figure 4).

We had insufficient data to formally test if formula and breast milk fed infants differed nevertheless there was no apparent difference in the above mentioned parameters between infants who were fed formula and those receiving expressed breast milk.

**Figure 4** Timing of TLESRs as expressed by the volume infused (panel A) and the percentage of feed infused (panel B). TLESRs occurred significantly earlier in the right lateral position (RLP) as compared to the left lateral position ( LLP), both, when expressed as the percentage of feed infused (indirect) as when expressed as volume infused (direct). Note that the volumes required to trigger the first TLESR sit within a closer range in the LLP than the RLP which is far more variable. Note also that the volume of the feed was only standardized within each infant, but not between infants. *p<0.01, paired T-test.

**DISCUSSION**

In this study we have shown that gastric infusion of very small volumes of liquid (feed) can lead to triggering of TLESRs. Furthermore in the RLP, when liquid pools just distal to the EGJ, TLESRs occur much earlier after the commencement of infusion. It seems unlikely that infused volumes as low as 0.3ml (figure 4, panel A) can realistically cause distension
or distortion of the gastric cardia of a degree sufficient to activate tension sensitive vagal afferent neurons located in the smooth muscle. Most infants began to trigger TLESRs with infusions within a very tight band of feed volumes in the LLP, whilst in the RLP feed volumes required to trigger TLESRs were both lower and considerably more variable. This interesting observation in terms of the variability of the response may indicate that, in the LLP, we have observed the stomach response to pure distension, whilst in the RLP, we have observed a combination of both the same stomach response and a secondary response related to the intragastric distribution of the feed relative to the EGJ. The latter would no doubt be more likely to vary from patient to patient since it would be dependent upon the exact depth of the catheter and where the feed ‘pooled’ upon initial infusion.

It could be argued that our results show the effect of posture and not so much of the infusion of the feed itself, because we did not record a pre meal baseline and are therefore unable to directly compare to a stable unfed state. However, in a previous study we have shown the rate of TLESRs in fasting (from the third post prandial hour onwards) healthy premature infants to be similar in RLP and LLP. We therefore believe that our findings are suggestive of the involvement of vagal mucosal chemoreceptors and/or mechanoreceptors in the region of the cardia or distal margin of the EGJ. These may putatively be involved in sensing of luminal contents and in turn modulation of the TLESR pathway. Vagal mucosal chemoreceptors, reacting to several medications and bile have been previously described in the mouse stomach. Also, vagal receptors combining properties of mucosal and mechanoreceptors, the tension/mucosal receptor, have been described in ferrets. However, there is no direct evidence from animal models that conclusively demonstrate involvement of these receptors in the vago-vagal TLESR pathway. It is important to recognize, however that TLESR-like LES relaxations (i.e. non-deglutitive LES inhibition) have already been demonstrated in relation to pharyngeal stimulation with minute amounts of water. We conclude that our experimental findings are suggestive of a similar mechanism localized in close proximity to the EGJ.

Physiologically, one would expect such a sensing mechanism to prevent rather than enhance liquid GER. More research is clearly needed to clarify the neuroregulatory mechanisms underlying our current observations and to examine differences between healthy subjects and patients with GER disease.

We have previously shown that gastric emptying is enhanced in the RLP, and therefore it could also be argued that, in the RLP, infused gastric contents may rapidly enter the duodenum leading to CCK release and earlier triggering of TLESR due to CCK mediated fundic relaxation in association with distension. We believe that this is an improbable explanation. Firstly, the degree of gastric distension is minimal in this experimental paradigm, and secondly the anatomical positioning of the stomach in the RLP favors pooling at the EGJ and therefore it is questionable that such low volumes can even reach the duodenum in such short time intervals. Ethically, we could not repeat our studies.
with the infusion of water to get a better understanding of the role of nutrients in the effect shown. However, it is important to recognize that the catheters themselves were continuously water perfused and therefore small volumes (12 ml/hr) were continuously being transported into the stomach via peristalsis. The fact that previous studies have not demonstrated any effect of body position on fasting levels of TLESRs, despite continuous water perfusion, suggests that the presence of nutrient is an important prerequisite for the manifestation of the positional effects seen. Our study might also have some clinical implications. Previous pathophysiological and clinical studies in infants with and without GER disease have focused on the post prandial period. For pH-metry studies, most analysis-software packages routinely leave out meal periods for analysis. Our results suggest that in infants, whether in RLP or LLP, most GER episodes occur during the meal, providing an explanation for the commonly observed feeding difficulties in infants with GER disease. Based on our results, it would be worthwhile to study if feeding, and especially tube feeding in LLP position has clinical advantages over feeding in supine position or RLP. Furthermore it suggests that more attention should be given to the feeding periods in 24 hour pH and pH/impedance studies in infants, especially in those children who present with feeding difficulties.

In conclusion, we have shown that in the RLP, when infused liquids are known to pool at the EGJ, minute amounts of liquid feed can trigger TLESRs in infants. These observations suggest that neuroregulatory mechanisms affecting the vago-vagal pathway leading to the occurrence of a TLESR are likely to be more complicated than previously thought. These mechanisms may involve sensing at the level of the EGJ in addition to sensing of tension within the gastric smooth muscle. Further studies are needed to establish the exact underlying mechanism(s) and whether these might have clinical implications for infants with symptoms suggestive of GER disease.

ACKNOWLEDGEMENTS

The authors would like to acknowledge Lisa McCall, Ros Lontis and Louise Goodchild for recruitment of eligible infants and their assistance during the studies.
REFERENCES


9 Trudgill NJ and Riley SA. Transient lower esophageal sphincter relaxations are no more frequent in patients with gastroesophageal reflux disease than in asymptomatic volunteers. Am J Gastroenterol 2001;96:2569-74.


