Pediatric gastroesophageal reflux and upper gastrointestinal tract motility: the use of multichannel intraluminal impedance and high resolution manometry
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Effect of body position changes on triggering of postprandial gastroesophageal reflux and gastric emptying in the healthy premature neonate

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ABSTRACT

Objective: To identify a body-positioning regimen that promotes gastric emptying (GE) and reduces gastroesophageal reflux (GER) one hour after feeding.

Study design: Ten healthy preterm infants (7 male, post menstrual age: 36(33-38) weeks) 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 one hour, position was changed to the opposite side. All infants were studied a second time with the order of positioning reversed.

Results: In the RLP there was more liquid GER than in the LLP (median (range): 9.5(6.0-22.0) vs. 2.0(0.0-5.0) episodes/hour, p=0.002). In the RLP first protocol, the number of liquid GER episodes per hour decreased significantly after position change (1st postprandial hour (RLP): 5.5(2.0-13.0) vs. 2nd post prandial hour (LLP): 0.0(0.0-1.0), p=0.002). GE was faster in the RLP first protocol than in the LLP first protocol (37.0+/-.21.1 vs. 61.2+/-.24.8 min, p=0.006).

Conclusion: A strategy of right positioning for the first postprandial hour with a position change to the left thereafter promotes GE and reduces liquid GER in the late postprandial period and may prove to be a simple therapeutic approach for infants with GER disease.
INTRODUCTION

Gastroesophageal reflux (GER) is very common in infancy and early childhood. In premature infants, both apnea and GER occur frequently, though the causal relationship between these events is controversial. Other typical GER symptoms, such as regurgitation, are normally mild and relatively harmless and therefore considered to be physiological. However, in a subgroup of infants, GER can cause more severe symptoms, such as feeding problems and failure to thrive, and complications such as esophagitis.

The acidity of GER episodes is thought to be a major pathophysiological factor in the development of these symptoms and complications. In infants, gastric contents are buffered by milk in the post-prandial period. Consequently, GER is likely to be weakly-acidic (4 < pH < 7) in the first hour after a meal, while acid GER (pH<4) occurs more often in the late post-prandial period.

In all age groups, transient lower esophageal sphincter relaxation (TLESR) is the major mechanism of GER, both in healthy subjects and in patients with GER disease (GERD). Of GER episodes triggered by TLESRs, a greater proportion is acidic in infants with GERD compared to asymptomatic controls. Gastric distension-induced stimulation of tension receptors, especially those in the very proximal stomach, initiates triggering of the TLESRs. This reflex is mediated via vagal afferent neurons, the nucleus tractus solitarius, and vagal efferent neurons (dorsal motor nucleus of the vagus nerve and nucleus ambiguous) and leads to regulated inhibition of the lower esophageal sphincter (LES), esophagus, pharynx and crural diaphragm thus allowing reflux to occur. The TLESR reflex has now been well described. However, recent observations show selectivity of triggering gas over liquid reflux in healthy controls and for acid over weakly-acidic GER in patients with GERD. Notably, slow gastric emptying does not correlate with the number of TLESRs triggered. This suggests that the mechanisms that regulate the threshold for triggering of TLESRs as well as the GER ‘type’ triggered by TLESRs appear to be more complex than can be explained by a single ‘stimulus-response’ mechanoreceptor reflex.

We recently studied the effect of left/right body positioning on GER and TLESR triggering in premature infants using combined impedance and manometry and showed that right-lateral positioning (RLP) was associated with an increased proportion of liquid reflux compared to left lateral positioning (LLP). This was probably due to the presence of gastric contents above the level of the esophago-gastric junction in this position, as demonstrated radiologically by Ewer et al. The overall triggering of TLESRs following feeding was significantly greater and GE of the feed was significantly faster in the RLP.

These paradoxical findings of increased reflux triggering in a setting of accelerated GE are difficult to explain based on gastric tension receptor-mediated triggering of TLESRs alone. Furthermore, these data suggest that postural interventions may be a useful non-pharmacological means of controlling both GE and GER.
The aim of the current study was to investigate the effects of changing body position on the triggering of TLESRs, GER and GE, in order to identify a positioning regime that would both promote GE and decrease the number of acid GER episodes occurring during the late postprandial period, when GER becomes more acidic.

METHODS

We studied ten preterm infants (7 male; 3 female) who did not experience any symptoms related to GERD or other gastrointestinal diseases and were healthy apart from their prematurity. All subjects were studied at the Women’s and Children’s Hospital in Adelaide, Australia. The subjects had a median gestational age of 31.5 (range: 27-36) weeks. Post natal age at time of the first study was 23 (11-62) days resulting in corrected age of 36 (33-38) weeks. The median weight at the time of the study was 2415 (2130 – 2800) g (table 1). For ethical reasons, all infants had to receive at least one of their daily feeds by gavage. The parents or 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.

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*Table 1. Demographics and randomization.* No: studynumber; PMA: post menstrual age (wks); PNA: post natal age (days); BW: birthweight (g); Weight: weight at first studyday (g); EBM: expressed breast milk; Volume: volume of feed (ml); Frequency: feeds/day; 1st protocol: protocol followed during first study day. RLP: right lateral position; LLP: left lateral position.

Measurement Techniques

*Esophageal impedance and manometry*

A combined multichannel intraluminal impedance and manometry catheter (outer diameter: 2 mm) that also allowed for gavage feeding was developed for the purpose of this study.
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 (3 side holes) and pharynx respectively. 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).

**Gastric emptying rate**

Gastric emptying rate was determined with the $^{13}$C-Na-octanoate breath test. This test has been described in detail elsewhere. In short, $^{13}$C labeled Na-octanoate was added to the infant's feed and breath samples were taken before the feed, at five minute intervals for the first 30 minutes after the start of the feed and at 15 minute intervals thereafter.
samples were analyzed for $^{13}$CO$_2$ content using an isotope ratio mass spectrometer. The $^{13}$CO$_2$ concentration in the breath samples was used to calculate the following GE variables: GE $t_{1/2}$, $t_{lag}$, $t_{max}$ and the GE coefficient (GEC), a general index for gastric emptying that takes into account the overall shape of the $^{13}$CO$_2$ excretion curve rather than the amount of $^{13}$CO$_2$ excreted at a given time point.\footnote{23}

**Experimental protocol**

All infants were studied twice on two consecutive days and subjected to two positioning protocols in a randomized cross over fashion (Figure 2). The assembly was passed transnasally into the stomach and positioned with the sleeve straddling the LES. The infants were then positioned in either the right lateral position (RLP) or left lateral position (LLP) and gavage fed their normal feed (expressed breast milk or formula). Feed volume was identical for both studies and the feed was infused by the same research nurse, who tried to keep the infusion velocity constant. One hour following the end of the feed, the infant’s position was changed to the opposite lateral side and motility and reflux recording continued for a further two hours.

**Figure 2. Experimental protocol.** Note that all infants were studied according to both protocols in a cross over fashion. The feeding time was dependent on the volume of feed primarily. RLP: right lateral position; LLP: left lateral position; PPH: postprandial hour
Data analysis
All details that could identify the subject and all information regarding the protocol were removed from each tracing before analyses. One investigator performed all analyses. In cases of uncertainty consensus was found with another investigator. Impedance tracings were analyzed for liquid, gas and mixed reflux episodes using established criteria. Manometry tracings were analyzed for TLESRs using criteria set by Holloway et al. If a GER episode was present on the impedance tracing without a TLESR present on the manometry tracing, the manometry tracing was then analyzed to determine the reflux mechanism involved. Manometry and impedance data were compared between the RLP and the LLP overall. For this purpose, data from the 1\textsuperscript{st} hour of the RLP first protocol were combined with the 2\textsuperscript{nd} and 3\textsuperscript{rd} hour of the LLP first protocol and these were compared to the data from the 1\textsuperscript{st} hour of the LLP first protocol and 2\textsuperscript{nd} and 3\textsuperscript{rd} hour of the RLP first protocol. In addition, all data were compared between the two protocols (figure 2) and between the first and second postprandial hour (PPH) in both protocols.

Statistical analysis
Normally distributed data are presented as means ± SD and are compared between the protocols or between sides using the paired t-test. 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. A p-value of less then 0.05 was considered statistically significant.

RESULTS
Feeding volumes and time
Feed volumes given to the infants were similar on both study days, ranging from 50 - 80 ml (median: 67.5 ml) and took 12.3 (7.5–36.2) minutes to administer by hand-driven syringe. The time taken to administer feeds was similar in the two protocols (RLP first: 13.1 (7.5-36.2) min vs. LLP: 12.3 (8.0-25.8) min., p=0.770).

RLP vs. LLP
More TLESRs and GER episodes were triggered while infants were in the RLP compared to the LLP (TLESRs: 9.5 (3.0-19.0) vs. 5.0 (3.0-17.0) respectively, p=0.020; GER episodes: 11.5 (6.0-24.0) vs. 7.0 (5.0-17.0) respectively, p=0.004). Liquid GER episodes were more frequent in the RLP compared to LLP (9.5 (6.0-22.0) vs. 2.0 (0.0-5.0) respectively, p=0.002). In contrast, the number of gas and mixed GER episodes was significantly lower in the RLP.
compared to LLP (gas: 0.0 (0.0-4.0) vs. 4.5 (1.0-10.0) respectively, p=0.012; mixed: 0.0 (0.0-2.0) vs. 1.0 (0.0-3.0) respectively, p=0.031). The relative contribution of liquid, mixed and gas GER to the total number of GER episodes was therefore significantly different between the two positions (figure 3).

Figure 3. Percentages of liquid, mixed and gas GER attributing to the total number of GER episodes on the LLP and the RLP. (Absolute number of GER episodes given in parentheses). GER: gastro-esophageal reflux; LLP: left lateral position; RLP right lateral position. * p<0.01; ** p<0.005, Wilcoxon’s matched pairs signed rank sum test.

RLP first protocol vs. LLP first protocol

The occurrence of TLESRs, as well as the number of GER episodes and the type of GER triggered over the study period differed between the two protocols (figure 4). All data for the two protocols are given in table 2.

When the RLP first and LLP first protocols were compared, the overall numbers of TLESRs and GER episodes triggered were similar. This also held true for the number of liquid, gas and mixed GER episodes (table 2).

More TLESRs were triggered in the first postprandial hour (PPH) in the RLP first protocol when compared to the LLP first protocol. This led to more liquid GER in the first PPH in the RLP first protocol. In the second PPH less liquid GER was triggered in the RLP first protocol compared to the LLP first protocol, although more gas GER was found (table 2). The total number of TLESRs was similar in both protocols during the second PPH. In the third PPH, liquid GER remained less prevalent in the RLP first protocol compared to the LLP first protocol, although the number of TLESRs and gas GER episodes were similar (table 2).
First vs. second postprandial hour

During the RLP first protocol, the number of TLESRs and the number of liquid GER episodes were significantly higher and gas GER episodes lower in the first hour (RLP) compared to the second (LLP) \((\text{figure 4} & \text{table 3})\). During the LLP first protocol the number of liquid reflux episodes was significantly lower while the number of TLESRs and gas GER episodes was similar in the first hour (LLP) compared with the second (RLP) \((\text{figure 4} & \text{table 3})\).

Gastric Emptying

Gastric half emptying time \((\text{GE}_{1/2})\) was significantly faster during the RLP first protocol when compared to the LLP first protocol \((37.0 +/- 21.1 \text{ vs. } 61.2 +/- 24.8, p=0.006 \text{ (figure 5 & table 4)})\).
Figure 4. Total number of TLESRs and GER episodes (liquid, mixed and gas) over time. X-axis is comprised of 10 minute periods, where 10 stands for 0-10 minutes, 20 for 10-20 minutes etc. GER: gastro-esophageal reflux; LLP: left lateral position; RLP: right lateral position.

Figure 5. Gastric emptying half time, RLP first protocol vs. LLP first protocol. RLP: right lateral position; LLP: left lateral position. *p=0.006, paired t-test.
**DISCUSSION**

This study shows that positioning healthy infants in the right lateral position (RLP) for the first postprandial hour (PPH) and in the left lateral position (LLP) afterwards virtually eliminates liquid reflux in the late postprandial period when gastric contents are acidic. At the same time it promotes GE. Furthermore, it suggests the presence of a neural mechanism modulating the gastric distension induced reflex that triggers TLESRs.

Overall, we found that more GER episodes were triggered in the RLP. Other studies have shown that symptomatic preterm and term infants have more esophageal acid exposure in the RLP compared to other positions as a result of more and prolonged episodes of acid GER.\(^{26,27}\) However, these studies did not investigate the underlying pathophysiological mechanisms. This increase during RLP is in accord with a recent study of healthy infants either in the RLP or the LLP, where we showed that more TLESRs are triggered in the RLP compared to the LLP.\(^{19}\)

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**Table 3. Median (range) number of TLESRs and GER episodes.** Data given for 1st PPH and 2nd PPH. RLP first protocol Difference between 1st PPH and 2nd PPH expressed as p-value (Wilcoxon’s matched pairs signed rank sum test). TLESR: transient lower esophageal sphincter relaxation; GER: gastroesophageal reflux; RLP: right lateral position; LLP: left lateral position; PPH: post prandial hour.

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<th>2nd PPH, LLP</th>
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<td>TLESR</td>
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<td>All GER</td>
<td>5.5 (2.0-15.0)</td>
<td>2.5 (1.0-6.0)</td>
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<td>Liquid GER</td>
<td>5.5 (2.0-13.0)</td>
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<td>Mixed GER</td>
<td>0.0 (0.0-2.0)</td>
<td>0.0 (0.0-2.0)</td>
<td>NS(1.000)</td>
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<tr>
<td>Gas GER</td>
<td>0.0 (0.0-2.0)</td>
<td>2.5 (0.0-6.0)</td>
<td>0.012</td>
</tr>
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</table>

**Table 4. Gastric emptying parameters, RLP first protocol vs. LLP first protocol.** Difference between RLP first and LLP first protocol expressed as p-value (paired t-test). RLP: right lateral position; LLP: left lateral position; GEC: gastric emptying coefficient.

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<th>LLP first</th>
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<td>T1/2</td>
<td>37.0 ± 21.1</td>
<td>61.2 ± 24.8</td>
<td>0.006</td>
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<td>Tlag</td>
<td>22.8 ± 6.7</td>
<td>27.0 ± 6.5</td>
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<td>Tmax</td>
<td>58.4 ± 13.4</td>
<td>74.1 ± 17.1</td>
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<td>GEC</td>
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In the present study, we have also shown that the proportion of liquid GER is much greater in the RLP compared to the LLP (87% vs. 26%). This difference was not only present in the first PPH, but became especially clear after the change in position to the left side. Turning infants from the LLP to the RLP was associated with a rapid increase in occurrence of liquid GER episodes. On the other hand, turning the infants from the RLP to the LLP stopped liquid GER and caused triggering of gas GER. It is now clear that this change in reflux type relates to the anatomical configuration of the stomach which makes it more likely that liquid will pool at the level of the EGJ in the RLP.

The current study has demonstrated that the change from left to right, as well as changing the type of GER triggered, also increased the total number of TLESRs and GER triggered. The opposite change from right to left had the opposite effect. Franzi et al showed in dogs that the threshold for distension induced triggering of TLESRs is lowest in the region of the stomach just distal to the esophagogastric junction. It could be argued that pooling of fluid at the EGJ region associated with a change to the RLP causes localized distension of the sub-cardiac region resulting in increased triggering of TLESRs. The opposite change to the LLP would result in pooling of fluid in the corpus and, although gas above the liquid would also distend the region just distal to the esophagogastric junction, the subsequent triggering of TLESRs and gas reflux would lead to greater depressurisation of the gastric lumen. Reduced capacity to vent gas and depressurize the stomach in the RLP could explain the rapid rise in TLESRs seen after the posture change to the right side. However, it should also be noted that GE rate also rapidly increased with the position change to the right. Although this increase in GE should assist in depressurizing the stomach, the triggering of TLESRs and GER is still increased. The opposite is the case with the position change to the LLP, where the triggering of TLESRs and GER decreases, whilst at the same time GE slows.

Clearly, the effects of position change on GER and GE are the direct result of alteration of the anatomy of the stomach and the intragastric distribution of contents relative to both the EGJ and pyloric outlet. However, it is difficult to reconcile our observations with the current understanding of the mechanism of control of TLESRs following a meal. This understanding is based on one predominant neural pathway and the initiation by one population of gastric tension receptors, whose stimulation should, at least in theory, be decreased if and when the contents of the stomach empty faster.

Gastric distension cannot therefore be the sole mechanism responsible for the control of triggering of TLESRs. The current and previous studies of this kind suggest the possibility of other, as yet un-described, regulatory mechanisms. These mechanisms may potentially involve mucosal receptors sensitive to direct contact of liquid luminal contents at the level of the EGJ. Recent data suggest that gas GER can be selectively triggered over liquid and mixed GER. Pandolfino et al recently found that diameter of the esophagogastric junction during opening probably plays a role in determining the nature of GER, but the proposed mucosal receptors might also be able to discriminate between different forms of gastric content. In animal models, several vagal mucosal mechano- and chemoreceptors have been
identified in the EGJ region.\textsuperscript{30,31} Alternatively, there may be mechanisms external to the stomach, perhaps localized to the crural diaphragm or gastric sling fibers, that are sensitive to the strain forces applied to the stomach and viscera during re-orientation associated with position change.

Our previous studies in premature infants with and without GERD indicated that the triggering of acid reflux in association with TLESRs was significantly greater in infants with GER disease.\textsuperscript{10,11} Therefore, control of acid GER in the late post-prandial period may be more therapeutically relevant than reducing non-acid GER in the early post-prandial period. These previous studies also showed no difference in GE between infants with or without GERD and therefore were equivocal with respect to the importance of delayed GE.\textsuperscript{10,11} It is, however, a widely held view that delayed GE is a feature of GERD and that delayed GE also exacerbates reflux in GERD patients.\textsuperscript{32-34} Delayed GE is also clearly a feature of feeding intolerance which may have a similar clinical presentation to GERD. Any treatment for GERD should therefore aim to reduce acid GER and accelerate GE. The current study indicates that this can be achieved in healthy infants by placing them in the RLP for one hour followed by a position change to the LLP. The efficacy of this simple positional intervention in infants with GERD needs to be assessed in a large randomized controlled trial. Such a study should compare our proposed regime with LLP only posturing, both with and without standard PPI therapy.
REFERENCES


Effect of body position changes on reflux in healthy premature infants


