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Effect of lateral positioning on gastroesophageal reflux (GER) and underlying mechanisms in GER disease patients and healthy controls

Short title

Effect of lateral positioning on reflux

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Abbreviations

CCK	Cholecystokinin
EGJ	Esophagogastric junction
GE	Gastric emptying
GER	Gastroesophageal reflux
GERD	Gastroesophageal reflux disease
HC	Healthy control
LES	Lower esophageal sphincter
LLP	Left lateral position
MII	Multiple channel intraluminal impedance
RLP	Right lateral position
SPECT	Single Photon Emission Computer Tomography
TLESR	Transient lower esophageal sphincter relaxation
WA GER	Weakly acid and weakly alkaline gastroesophageal reflux

Keywords

GERD, motility, esophagus

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ABSTRACT

Background

Posture has been shown to influence the number of transient lower esophageal sphincter relaxation (TLESRs) and GER, however the physiology explaining the influence of right lateral position (RLP) and left lateral position (LLP) is unclear. The aim of this study was to determine the influence of RLP and LLP on TLESRs and GERD after a meal in GER disease (GERD) patients and healthy controls (HC) while monitoring gastric distension and emptying.

Methods

Ten GERD patients and ten HC were studied for 90min (30min test meal infusion, 30min post-prandial in either RLP or LLP (randomly assigned) and 30 min in alternate position). The study was repeated on a separate day in reverse position order. TLESRs, GER and gastric empting rate were recorded using manometry, multichannel intraluminal impedance and ^{13}C-octanoate breath tests. Gastric distension was visualized by five serial gastric volume scintigraphy scans during the first 30 min.

Key results

GERD patients had increased numbers of TLESRs in RLP compared to LLP in the first postprandial hour (5(4-14) and 4.5(2-6) respectively, p=0.046) whereas the number of TLESRs was not different in RLP and LLP (4(2-4) and 4(3-6) respectively, p=0.7) in HC. Numbers of GER increased similar to TLESRs in GERD patients. In GERD patients gastric emptying reached peak $^{13}CO_2$ excretion faster and proximal gastric distension was more pronounced.

Conclusion & Inferences

In GERD patients, TLESRs, GER, distension of proximal stomach and gastric emptying are increased in RLP compared to LLP. This effect is not seen in HC.

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INTRODUCTION

Gastroesophageal reflux (GER) occurs in both patients and healthy controls. When GER causes symptoms or complications it is referred to as GER disease (GERD) ((1, 2)). The most important underlying mechanism of GER is transient lower esophageal sphincter relaxation (TLESR), a vago-vagally mediated relaxation of the lower esophageal sphincter (LES) and the crural diaphragm ((3-7)). These structures form the esophagogastric junction (EGJ), the main anti reflux barrier. TLESRs are a physiological mechanism thought to allow gas to vent from the stomach ((7)). There is no clear difference in the number of TLESRs in HC or GERD patients, however TLESRs are more likely to be associated with liquid and acidic GER in GERD patients ((8-11)).

Several factors are known to trigger TLESRs ((12)). Stretch receptors located in the proximal stomach trigger TLESRs via a vago-vagal pathway ((6, 13)). These receptors are activated after a meal due to a combination of gastric distension and gastric accommodation, caused by mechanic distension after volume increase, the reduced gastric tone and enhanced gastric compliance as a response to food intake ((14, 15)).

Another factor influencing TLESRs, is cholecystokinin (CCK). CCK is released when nutrients (especially fat) enter the duodenum, causing a decrease in LES pressure, fundic relaxation and an increase in TLESRs ((16, 17)). This effect can be blocked by a CCK-A antagonist(17). The increase in TLESRs after a meal is most likely modulated by both fundic relaxation and by direct interaction of CCK with the vagal afferent system.

It has been shown that lateral positioning affects TLESR triggering, although not significantly in all studies ((18-21)). In GERD patients and healthy adults, TLESRs and GER have been shown to occur more frequently in right lateral position (RLP) compared to left lateral position (LLP) ((19, 21)). Recently, we showed that TLESRs occurred more frequently and were more likely to cause liquid GER in RLP in healthy premature infants, despite more rapid gastric emptying ((22, 23)). Additionally,

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small volumes of a liquid meal caused a significantly faster onset of TLESR triggering after the start of a meal infusion in RLP compared to LLP ((24)).

The underlying mechanisms of these observations are not completely understood. The effects of body positioning in adults may provide more insights into factors that are known to influence TLESR triggering. These factors include the activation of the stretch receptor by distension and accommodation of the stomach, distribution of gastric contents within the stomach and the rate of gastric emptying, all of which are likely to be influenced by different body positions. Based on the above, we hypothesize that the increased number of TLESRs in RLP compared to LLP could be caused by more rapid emptying of nutrients in RLP due to the anatomical position of the lesser curvature, difference in activation of stretch receptors, pooling of gastric contents in the proximal stomach or a combination of these factors. Furthermore we hypothesize that interaction of the involved factors may be disrupted in GERD patients.

In this study, we investigated the influence of lateral positioning on the onset of TLESRs and the type of GER after a test meal in both adult GERD patients and healthy adult controls while simultaneously monitoring potential underlying of mechanisms of gastric distension and gastric emptying.

METHODS

Subjects:

Ten GERD patients and ten healthy controls (HC) were included. GERD patients were required to meet ≥ 2 of the following criteria: 1) experience heartburn and regurgitation for >3 months and >2 times a week, 2) diagnostic pH monitoring with acid exposure in the distal esophagus of >5,8% ((25)), 3) combined pH MII monitoring with a SAP>95% or 4) reflux esophagitis ≥grade 1 confirmed by endoscopy. GERD patients ceased any anti reflux and prokinetic medication 5 days prior to the study. HC had no history of GERD or symptoms related to GERD. Subjects, who had undergone previous gastrointestinal surgery (with exception of appendectomy), congenital abnormalities affecting the

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gastro-intestinal tract, neurological impairment, known large hiatus hernia (>3cm), were pregnant and/or had any condition making discontinuation of anti-reflux medication impossible, were excluded.

Subjects provided a written informed consent and the protocol was approved by the Medical Ethics Committee of the Academic Medical Center, Amsterdam.

Experimental protocol

Patients and controls completed a validated GERD questionnaire (Reflux Disease Questionnaire, RDQ) prior to commencement of the study ((26)). Subjects were studied twice on separate days and underwent both positioning protocols in a randomized cross over fashion, either LLP or RLP first. Study procedures were identical for both GERD patients and HC.

Study procedure (Figure 1)

Subjects fasted for at least 6 hours prior to the commencement of the study. Thirty - forty minutes prior the start of the study, subjects received an intravenous injection with ^{99m}Tc-pertechnetate. An assembly of a manometry and pH-MII catheter was transnasally positioned under topical nasal anesthesia with the sleeve sensor straddling the LES. Subjects were then randomly positioned in either LLP or RLP in the Single Photon Emission Computer Tomography (SPECT) scanner and baseline gastric volume was assessed during the first SPECT scan. After the baseline SPECT scan, a liquid test meal (Nestle nutrition Isosource Protein, 512kJ, 14 gr carbohydrate, 6 gr protein, 4 gr fat per 100 mL) was infused in the stomach, at a constant rate, initially of 100mL during the first 15 minutes (slow infusion) followed by 300mL during the next 15 minutes (fast infusion). During the meal infusion four SPECT scans were taken (two during slow and two during fast infusion). Furthermore, the ^{13}C Na-Octanoate breath test was performed. After 60 minutes, 30 minutes after the end of the meal infusion, subjects changed over to the other lateral position for 30 minutes.

Recording methods and raw data analysis

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Manometry and esophageal impedance

A water perfused manometry catheter with 8 esophageal channels spaced 3 cm apart, a 7 cm sleeve, a gastric channel and a central lumen allowing liquid meal infusion and a single use pH-MII catheter (Unisensor pHTip ™disposable catheter) were used. The manometric assembly was positioned with the tip in the stomach and the sleeve straddling the high pressure zone at the EGJ. The pH-MII catheter was placed in the esophagus with its pH sensor 5 cm above the proximal border of the manometricly established high pressure zone. Data acquisition and analysis were performed using the Stationary Solar Gastro System (MMS Inc., Enschede, The Netherlands).

All pH-MII tracings were analyzed for GER episodes, which were qualified as liquid, mixed or gas and acidic (pH<4), weakly acidic (4<pH<7) or weakly alkaline (pH>7) according to accepted standards ((9, 27, 28)). For analysis, liquid and mixed GER episodes were grouped (liquid/mixed GER) as well as weakly acidic and weakly alkaline GER (WA GER). Manometry tracings were analyzed for TLESRs and LES resting pressure. The data were analyzed for different periods: slow infusion, fast infusion, total infusion, postprandial period first position (30-60 min), postprandial period second position (60-90 min).

Gastric emptying breath test (GEBT)

To assess gastric emptying rate, a ^{13}C Na-Octanoate breath test (GEBT) was performed. 100mg ^{13}C labeled Na-Octanoate (a stable isotope) was added to the liquid study meal by injecting it as a bolus within 1 minute at the start of meal infusion. Breath samples were taken at 1-minute intervals during the first 15 minutes of the study and at 5 minute intervals during the remaining 75 minutes. Obtained breath samples were analyzed for the ratio between $^{12}CO_2$ and $^{13}CO_2$ content using an isotope ratio mass spectrometer. $^{13}CO_2$ concentration was used to calculate gastric emptying time as previously described ((29)). Three parameters to express gastric emptying time were used; time to reach peak ^{13}C excretion (Time to Tmax), the maximum ^{13}C excretion (%dose ^{13}C at Tmax), a fitted

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curve was made and the slope of the onset of ^{13}C excretion (GEonset) was calculated as %dose ^{13}C at Tmax/ Time to Tmax.

Gastric distension SPECT scans and assessment of gastric acid distribution

Gastric mucosa was labeled with 200 MBq 99mTc-pertechnetate, a monovalant negatively charged molecule accumulated and secreted by the gastric parietal cells, closely in parallel with gastric acid secretion. This was previously used and validated to visualize gastric volume change (as a marker for gastric distension and accommodation) and intragastric acid distribution on Single Photon Emission Computer Tomography (SPECT) ((30-32)).

Subjects were positioned in lateral position on the imaging table of a large field-of-view (GE Infinia II, 's Hertogenbosch, The Netherlands) gamma camera equipped with low-energy high-resolution collimators with the stomach in the middle of the field-of-view. Five fast SPECT scans were acquired (7 minutes, 72 views, 10 sec/view, 128x128 matrix). After completion of the acquisition data were reconstructed on a Hermes computer (Hermes Medical Solutions, Stockholm, Sweden).

From the acquired SPECT scans, the fasting (baseline) gastric volume was calculated as previously described ((33)). Total, proximal (fundus) and distal (antrum) gastric volume change were calculated relative to baseline volume as a marker of activation of stretch receptors through gastric distension and accommodation. Throughout the manuscript this will be referred to as gastric distension.

On the fifth scan, the distribution of gastric acid was analyzed visually to assess patterns of gastric acid pooling.

Data analysis

Analysis was performed blinded to the identity of the subject (GERD patient/HC) and position of the subject (LLP/RLP). Data of the first hour postprandial was grouped, including the postprandial period first position (30-60 min) of the first study and the matching lateral position of the postprandial period (60-90min) of the second study.

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Time to first TLESR after the start of the liquid test meal infusion, numbers of TLESRs and GER episodes, the type (acidic, WA) of GER episodes, gastric emptying time and gastric distension (total, proximal and distal) were compared between groups (GERD patients vs. HC) and position (LLP vs. RLP). Furthermore, correlations between TLESRs, GER, gastric emptying and gastric distension were assessed.

Statistical analysis

As the data were non Gaussian, all parameters were described using medians and interquartile ranges (IQR) unless otherwise stated and were compared using the Wilcoxon's signed rank test for paired data and the Mann-Whitney-U for non paired data. Dichotomous data were analyzed using a Fisher's exact test. Correlations were calculated using Spearman's correlation. A p-value <0.05 was considered to be statistically significant.

RESULTS

Subjects

Ten GERD patients (7 male, median (range) age: 31 (18-57) years, median (range) BMI: 24 (21-29)) and ten healthy controls (4 male, median (range) age: 22 (19-57) years, median (range) BMI: 23 (19-28)) were included in the study. BMI was not different between the groups ($p=0.39$). One GERD patient did not complete the study protocol due to severe nausea and vomiting when turning to RLP. Data obtained during the first hour of his study in both RLP and LLP are reported. All HC completed the study protocol without problems. HC had median (IQR) RDQ scores of 0 (0-0). The GERD patients had a median RDQ score of 15 (9-21). One GERD patient had a hiatal hernia of <3 cm as diagnosed by endoscopy.

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Onset of TLESRs after infusion start

The time of onset of the first TLESR after the constant infusion of a liquid meal was comparable between GERD patients and HC both in LLP (25 (10-43) vs. 19 (1-36)min) and RLP (24(9-39) vs. 23(4-41)min). Time of onset of TLESRs did not correlate with gastric emptying or gastric distension.

Postprandial TLESRs and GER

GERD patients had an increased number of TLESRs in the first postprandial hour in RLP compared to LLP (5 (4-14) and 4.5(2-6) respectively, p=0.046) whereas HC did not exhibit this difference between RLP and LLP (4 (2-4) and 4(3-6) respectively, p=0.7) (Figure 2). The difference in TLESRs and GER episodes in RLP between GERD patients and HC did not reach statistical significance (p=0.089 and p=0.123 respectively). In GERD patients the majority of GER episodes were liquid/mixed irrespective of position, whilst in HC, LLP was associated with significantly less liquid GER (47% (11-69%) of liquid/mixed GER compared to 80% (73-100%) in RLP, p=0.015 (Figure 3). In both LLP and RLP, GERD patients have more acid GER episodes (LLP and RLP combined: 2(2-5) vs. 0.5(0-1), p=0.008) and more liquid/mixed GER episodes (5(4-14) vs 3.5(1-7) p=0.01) compared to HC.

Gastric empting

Gastric emptying reached peak ^{13}C -excretion faster in RLP compared to LLP in both GERD patients (Time to Tmax in RLP: 36 (26-46) min and in LLP: 49 (41-74) min respectively, p=0.007) and HC (Time to Tmax in RLP: 43 (35-54) min and in LLP: 48.5 (43-73) min respectively, p=0.017). In RLP GERD patients had a significantly faster GE onset (p=0.008) and Time to Tmax is shorter (p=0.028) compared to HC (Figure 4, gastric emptying curves). In LLP no difference was found between HC and GERD patients.

LES pressure

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LES pressure was reduced significantly in the first postprandial 30 minutes in RLP (from 11(8-15) mmHg to 7(4-12) mmHg after infusion, p=0.007) and in LLP (from 11(10-17) mmHg to 10(6-15) mmHg after infusion, p=0.004). There were no significant differences between HC and GERD patients in LLP or RLP. When starting in RLP, LES pressure (from 11 (9-13) to 9(7-13) mmHg, p=0.55) did not change after turning to LLP. Alternatively, turning from LLP to RLP resulted in a decrease of LES pressure (from 10 (5-18) to 7(4-10) mmHg, p=0.001) in all patients.

Gastric distension and acid distribution

When assessing the whole stomach, more gastric distension was observed in LLP compared to RLP (ratio scan 5 vs scan 1 in GERD patients and HC combined, p=0.05). GERD patients exhibited a more pronounced increase in distension in RLP than HC. GERD patients had significantly greater distension of the stomach compared to HC after slow infusion (p=0.015) and during the start of the fast infusion (p=0.023). Interestingly, proximal stomach distension was significantly enhanced during the last scan in RLP in GERD patients compared to HC, p=0.034 (Figure 4, Proximal gastric distension curves).
On the fifth scan, the distribution of gastric acid was analyzed visually to assess patterns of gastric acid pooling. Two distinct patterns were observed; one pattern with a proximal and distal acid pool (two high pertechnetate signal intensity zones) and one pattern with one acid pool (one high pertechnetate signal intensity zone) (Figure 5). The fifth scan of every study was classified into one of these two patterns. These patterns were significantly different (Fisher's exact test p<0.001) in LLP compared to RLP in both GERD patients and healthy volunteers. Pattern one (proximal and distal pooling of acid, Figure 5A) was observed in 16 of 20 scans in LLP, while pattern two (one homogenous acid pool, Figure 5C) was observed in 20 of 20 scans in RLP. There was no difference between GERD patients and HC.

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DISCUSSION

In this study we have shown that the effect of lateral position on GER and its underlying mechanisms is significantly different in GERD patients compared to HC. Body position is known to increase the number of TLESRs and GER in RLP ((21, 23)). We indeed observed that TLESRs and GER are more prevalent in RLP in GERD patients, however, this effect was not observed in HC. We also observed more rapid gastric emptying in the RLP in both GERD patients and HC with GERD patients having more rapid early gastric emptying. Furthermore we demonstrate, that post-prandial proximal gastric distension in RLP is more pronounced in GERD patients.

In line with our previous studies investigating the influence of lateral positioning on gastric emptying and GER in premature infants ((22, 23)), we demonstrated that in RLP the incidence of GER is increased while gastric emptying is accelerated.

Gastric emptying was measured by adding the 13C octanoate marker at the beginning of the infused test meal. This experimental setup was chosen to measure the onset on gastric emptying most accurately. In LLP the onset of gastric emptying was later than in RLP. This may have allowed the octanoate to dilute in the meal, leading to a more delayed measurement of an increase in octanoate (34). Passive factors such as gravity or buoyancy may have had an delaying effect on the early emptying phase in LLP due to independent effects of position on gastric function (35). However, in this study protocol we were most interested in the onset of gastric emptying the difference between GERD patients and HC in the respective positions. The onset of gastric emptying is less influenced by the dilution of the marker in the meal supported by the fact that there was no significant difference in the onset of gastric emptying in LLP compared to RLP. Furthermore the difference between GERD patients and HC was observed in RLP.

An increase in TLESRs and GER, in a setting of accelerated GE may be explained by the now well characterized mechanism of gastric distension following nutrient presentation to the duodenum. This

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may largely be due to CCK release which is known to decrease LES pressure and augment gastric distension, the latter mechanism enhances TLESRs ((16)). However, CCK can also down regulate gastric emptying (17) via stimulation of isolated pyloric pressure waves and increase basal pyloric tone (36, 37). This response may explain the convergence of the gastric emptying curves of GERD compared to those of the HC in the 30-60 minutes following the meal infusion in RLP (Figure 4B). Although gastric emptying rate differences may influence CCK release, we did not measure serum CCK in this experiment and therefore we are unable to draw further conclusions with respect to the precise role of CCK and other gut hormones.

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. This clinical impression is widespread and has led to prokinetic agents being used to treat GER symptoms despite the lack of evidence for its effectiveness ((38)). ~~The findings of this study underline the need to reassess the role of prokinetics for the treatment of GERD.~~ This findings of this study do not support the rationale for the use of prokinetics in the treatment of GERD, it should however be recognized that this study was not performed in a physiological setting and our study design differed from standard test settings. Prokinetics may have a more complex, yet unknown, effect on gastric function and GERD.

The increase in gastric distension of the whole stomach after constant infusion of a liquid meal was more pronounced in LLP compared to RLP and there was no difference between GERD patients and HC. However, the proximal gastric distension was significantly greater in RLP compared to LLP in GERD patients as has been observed by others ((38-40)). The increased distension in GERD patients may have contributed to the increased numbers of TLESRs although this effect was less pronounced ($p=0.089$). Not only distension of the proximal stomach but also distension of the EGJ has been reported to play a role in GER. Pandolfino et al showed that the EGJ is more compliant in GERD

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patients than in controls ((41)). They propose that the anatomic degradation leading to wider opening of the EGJ during TLESRs may partly explain the difference in the type of the refluxate between GERD patients and controls. This hypothesis could explain our finding of TLESRs resulting in more liquid GER in GERD patients in RLP.

Van Herwaarden et al ((21)) observed that HC had increased TLESRs and GER in RLP, whereas we did not show a difference in TLESR in RLP vs. LLP in our HC group. This discrepancy may be explained by differences in the protocols used. Van Herwaarden studied patients over a longer period and incorporated a refluxogenic meal, both resulting in more GER events in the subjects they studied.

Our results also differ with the papers by Mittal and Sifrim in which the authors report that TLESRs are equally frequent in GERD patients and HC ((10, 42, 43)). Whilst not statistically significant, we observed a trend towards TLESRs being more frequent in RLP in GERD patients than in controls. It is important to note that the studies which originally described TLESR as a reflux mechanism, also reported greater numbers of TLESRs in GERD patients vs. controls ((3-5)). In these and subsequent studies subjects stayed in recumbent position or undergoing 24 hr measurement, TLESRs were more prevalent in GERD patients than in HC ((44, 45)). In contrast, subjects in the studies of Sifrim and Mittal were studied in sitting position, possibly explaining the different findings in those studies.

Gastric acid distribution has been suggested to be an important determinant of the type of GER in GERD patients and HC ((32, 46-49)). We observed a distinct different pattern of ^{99m}Tc-pertechnetate pooling as a marker of gastric acid in LLP vs RLP, with more pooling in the proximal and distal stomach in LLP suggesting that the acid pool floats on top of the gastric contents. Our experimental setting was not specifically designed to measure pooling of gastric acid and therefore we were unable to visualize the position of the acid pool in relation to the EGJ. However, our results indicate that the location of the acid pool is dependent on body position.

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There are some limitation to this study. The study groups are relatively small, although the robust crossover design yielded significant differences between the groups. Furthermore, this study was performed in non-physiological test settings. It is important to recognize the benefits and limitations of this setting. The two-phase infusion protocol was chosen for the following reasons; the initial, slow phase was designed to ensure accurate measurement of the first onset on gastric emptying. The second, more rapid infusion rate was chosen to promote gastric distension and therefore the triggering of TLESRs due to this mechanism. This design may have promoted more pronounced differences in onset of gastric emptying and in number of TLESRs.

In conclusion, TLESRs, GER, distension of proximal stomach and gastric emptying are increased in RLP in GERD patients compared to HC. The underlying mechanism for these effects may relate to increased gastric distension in RLP enhanced by more rapid delivery of nutrients to the duodenum in GERD patients and possibly by pooling of gastric contents in the fundus in RLP. ~~Whilst controversial, these data suggest that the role of GE in GERD, in particular slowing of GE, may be worthy of further investigation~~ There was no difference in time to onset of GER between GERD patients and HC or RLP and LLP nor did we observe a correlation with gastric emptying or gastric distension suggesting the interaction between these factors may be not be explained by a simple model. Furthermore this study suggests that the interaction of the factors regulating the number of TLESRs may be disrupted in GERD patients. In future studies investigators should carefully consider positioning of the study subject as this study suggests that differences between HC and GERD patients are most pronounced in RLP.

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Figure 1. Study protocol. Subjects were randomized into LLP first or RLP first prior to the first study. Subjects were studied a second time following the same protocol, starting in the alternate position. GEBT: Gastric empyting breath test. GA: Gastric accommodation scans. B.L.: baseline

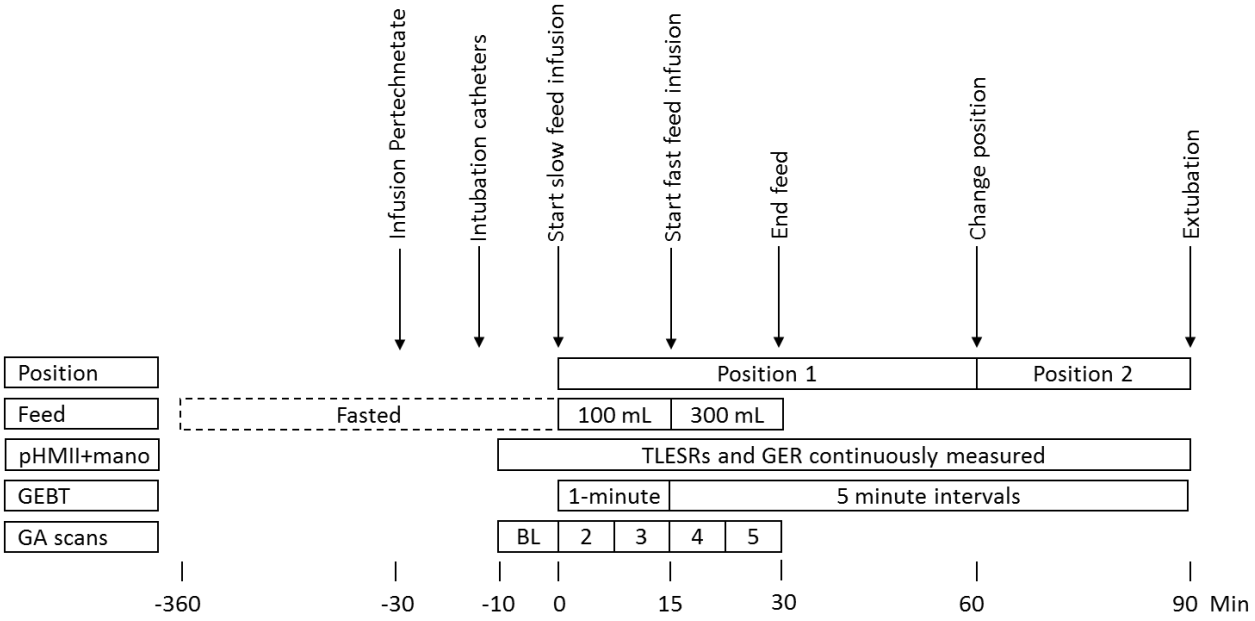

Fig 2. TLESRs in GERD patients and healthy controls (HC) in right lateral position (RLP) and left lateral positions (LLP). The number of TLESRs is highest in RLP in GERD patients.

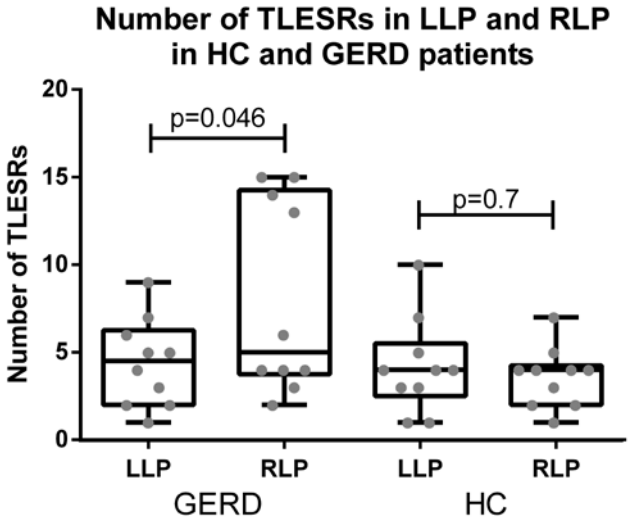

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Figure 3. GER and TLESRs. Cumulative number of TLESRs and GER in HC and GERD patients during the slow infusion (SI), fast infusion (FI) and in the first postprandial hour (PP)

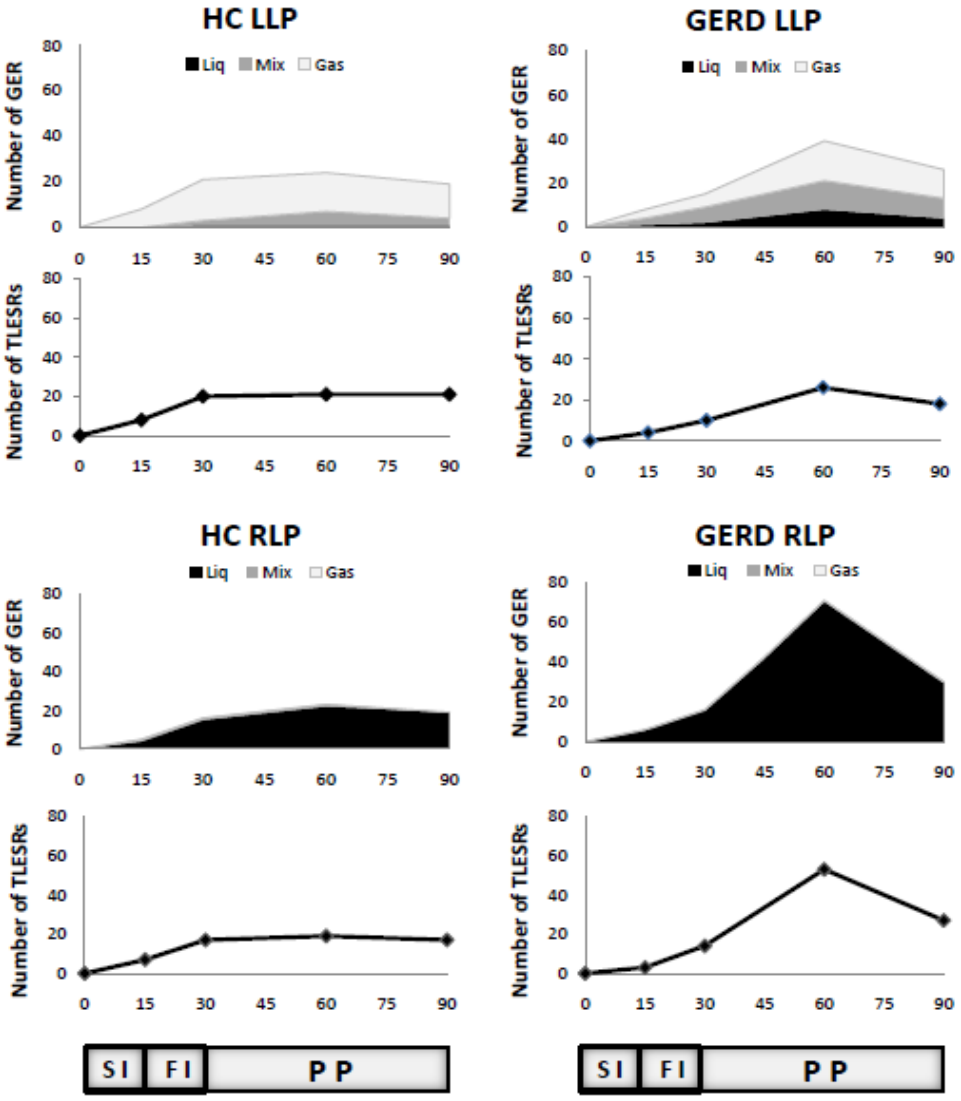

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Figure 4. TLESRs, GE and GD curves. Cummulative number of TLESRs (figure **4A**), Gastric emptying (GE, figure **4B**) and Proximal gastric distension (GD, figure **4C**) during flow feed infusion (SF), fast feed infusion (FF) and 30 minutes post prandial. Full line = GERD patients, dotted line = HC. *p<0.05

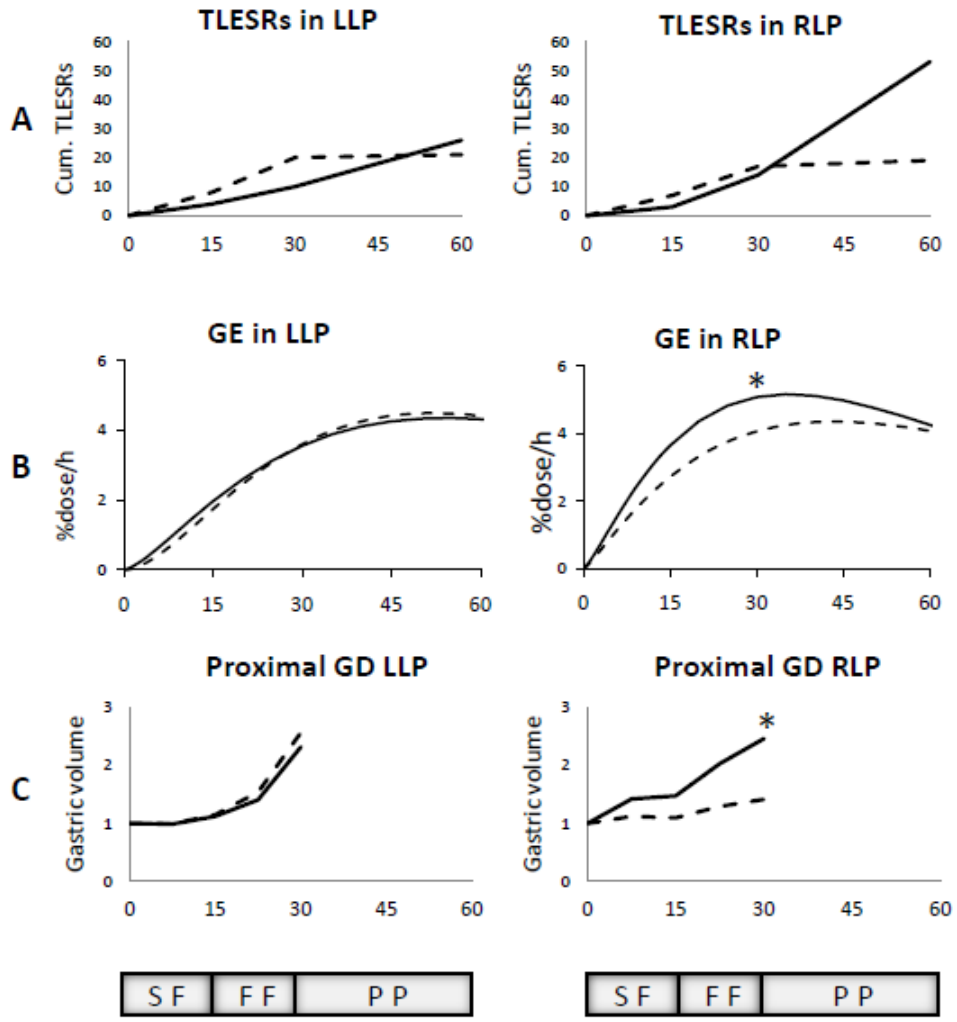

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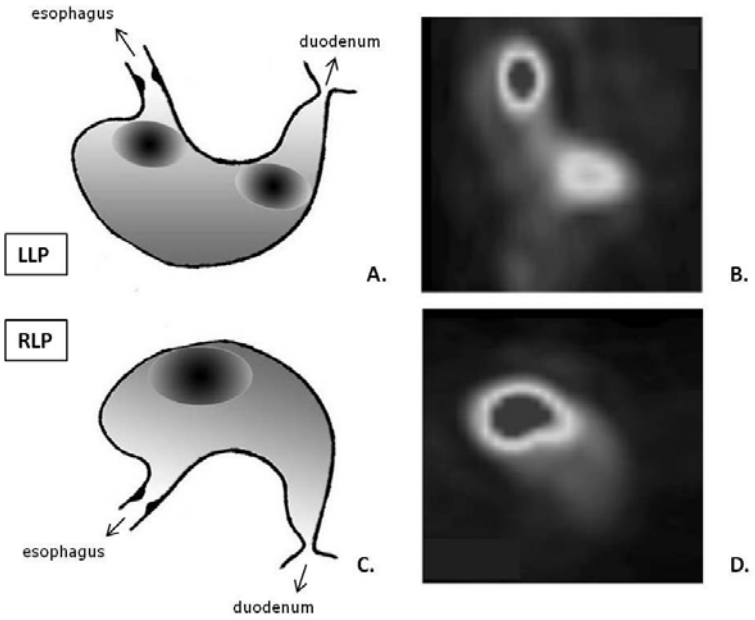
Figure 5. Acid pooling. Different patterns of acid distribution in LLP and RLP. Figure **5A** and **5C** are graphic views for anatomical orientation of the SPECT scan images (**5B** and **5D**). In the SPECT images the light grey represents the liquid test meal and the dark grey represents the acid pool. In LLP (**5A** and **5B**), acid accumulates in the proximal and distal stomach, whereas in RLP, there is only one acid pool presumably in the fundus/cardia of the stomach.



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