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Published in:
Gut

DOI:
10.1136/gut.51.4.475

Citation for published version (APA):

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Gut 2002;51:475-479
doi:10.1136/gut.51.4.475

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Mechanisms of gastro-oesophageal reflux in preterm and term infants with reflux disease

T I Omari, C P Barnett, M A Benninga, R Lontis, L Goodchild, R R Haslam, J Dent, G P Davidson

Gastro-oesophageal reflux disease (GORD) is common in infants and causes irritability, frequent vomiting, apnoea, aspiration pneumonia, and failure to thrive. Recent studies in healthy preterm infants have shown that transient lower oesophageal sphincter relaxation (TLOSR) is the predominant mechanism of GOR. There is still debate as to whether in patients with GORD, TLOSRs occur at a similar rate to normal subjects, but are more often associated with the occurrence of acid reflux. Pathophysiological mechanisms of GORD have not been studied in preterm and term infants and there are no published data in these patients. Delayed gastric emptying (GE) may be present in infants, but a previous study which correlated GE and reflux parameters in infants showed no relationship. Improvement of GE, in addition to increased salivary secretion, LOS tone, and oesophageal motility, is one rationale for prokinetic therapy although recent studies have been unable to demonstrate acceleration of GE with cisapride.

The aim of this study was to use simultaneous pH monitoring, oesophageal manometry recording, and GE assessment to characterise the motor mechanisms responsible for GOR in premature and term infants with and without GORD.

MATERIALS AND METHODS

Subjects

The study was approved by the ethics committee of the Women's and Children's Hospital and informed consent was obtained before each study. Studies were performed in 36 (16 male and 20 female) infants with a mean postmenstrual age of 36±2 weeks (range 33–40). Mean infant weight was 2079 g (range 1480–2840). Sixteen infants were receiving xanthine treatment for apnoea of prematurity. Gavage (tube) feeds were of non-fortified expressed breast milk (EBM) in 22 infants and 14 were receiving infant formula (Enfalac 20 or 24 calorie/ml; Mead Johnson, Canada). Infants received bolus feeds at two (n=7), three (n=19), or four (n=10) hour intervals.

Patient grouping

The normal (control) group in this study consisted of 22 infants who were healthy for relative gestational age with no history of feeding problems and/or GOR. These infants were compared with a group of 14 symptomatic infants with GORD who had been seen from birth by one physician (their consistent medical care giver). The research team was notified in cases where an infant was experiencing feeding problems and/or reflux based on a symptomatic profile (feed problems, vomiting, irritability, xanthine resistant apnoea, weight loss) and an intention to treat using conservative therapy (feed thickeners, postural changes, antacids) and/or pharmacotherapy (cisapride, ranitidine).

All infants, in both the normal and GORD groups, were further evaluated using a GOR symptom assessment chart. Symptoms were recorded from the time of consent to the start of the manometric study (period of 2–7 days). The GOR chart allowed for the recording of feeding times and the frequency of (i) vomiting, (ii) apnoea, (iii) choking, and (iv) behavioural changes (that is, irritability/fussing, back arching, grimacing, gagging). Staff responsible for routine care of the infants completed the chart whenever these events were observed. Symptom frequency (total number of symptomatic events

Background: Transient lower oesophageal sphincter relaxation (TLOSR) is the predominant mechanism of gastro-oesophageal reflux (GOR) in healthy infants but the mechanisms of GOR in infants with GORD disease (GORD) are poorly understood.

Aims: To measure the occurrence of TLOSR, GOR, and gastric emptying (GE) rate in preterm and term infants with GORD.

Patients: Thirty six infants were studied and grouped as normals or GORD based on a routine clinical assessment and confirmation of an assessment of GORD by reflux symptom charts and oesophageal pH monitoring.

Methods: A micromanometric assembly incorporating a micro pH electrode recorded oesophageal motility and pH. GE rate was determined using the 13C-octanoic acid breath test.

Results: TLOSR was the predominant mechanism of GOR, triggering 50–100% of GOR episodes (median 91.5%). Abdominothoracic straining significantly increased the occurrence of GOR in association with TLOSR. In infants with GORD, the number of TLOSRs overall was similar to normals but the proportion of TLOSRs accompanied by acid GOR was significantly higher than in normals (16.5% v 5.7%, respectively; p<0.001). Infants with GORD had a similar GE rate to normals.

Conclusions: In infant GORD, acid reflux associated TLOSRs are abnormally common and likely to be a major contributing factor to the pathophysiology of GORD. Infants with GORD do not have delayed GE.

Abbreviations: LOS, lower oesophageal sphincter; TLOSR, transient LOS relaxation; GOR, gastro-oesophageal reflux; GORD, GOR disease; GE, gastric emptying; EBM, expressed breast milk.
recorded divided by the number of days of charting) was
determined by chart analysis.

Twenty four hour oesophageal pH monitoring in GORD
patients was carried out using the Medtronic “Digitrapper”
pH monitoring system (Medtronic, Salt Lake City, Utah, USA)
and the pH probe (Medtronic 24 ME, diameter 1.5 mm) was
located 3 cm above the LOS as previously described
\(10\). The reflux index (% time pH <4) was determined using the
“Esophagram” analysis program.

The presence or absence of ongoing symptoms was
evaluated three months after discharge by completion of
Orenstein’s “I-GERQ” reflux questionnaire.\(^{11}\)

**Manometric technique**

Patterns of oesophageal motility were recorded with a micro-
manometric feeding assembly (2 mm od) which incorporated
a sleeve sensor for LOS pressure measurement.\(^2\)\(^-\)\(^4\) The core
channel of the assembly was used for gavage feeding. Oesophageal pH was monitored with an antimony micro pH
electrode od 0.3 mm (Microelectronics Department, University
of South Australia, South Australia) installed within one
of the assembly lumina and emerging 3 cm proximal to the
centre of the LOS sleeve. Data acquisition and analysis were
performed on a Macintosh Quadra 700 with software based on
National Instruments’ Labview (MAD software, Royal Ad-
daile Hospital, C Malbert).

**Manometric protocol**

The assembly was positioned with the mid point of the sleeve
straddling the LOS. After positioning and with the infant in
the right lateral posture, the feed was gavaged over 15–30
minutes. Oesophageal pH and spontaneous oesophageal body
and LOS motor patterns were then recorded during the feed
and for four hours.

**Analysis of manometric and pH tracings**

Analyses were performed by investigators (TO and MB) who
were blinded to the clinical status of the infants. Swallow
related LOS relaxations and TLOSRs were defined using previ-
ously described criteria.\(^4\) A common cavity reflux episode (fig
1) was defined as an abrupt sustained increase (\(> 2\) mm Hg)
in intraluminal pressure to equal intragastric pressure. Abdominothoracic straining was identified by sustained
increases (\(> 5\) mm Hg) of intragastric pressure for at least 10
seconds, associated with a corresponding rise in oesophageal
body pressure. In practice, strain events shorter than 10
seconds occurred infrequently and were excluded. The

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**Figure 1** Example tracings of transient lower oesophageal sphincter relaxations (TLOSRs) triggering (A) acid gastro-oesophageal reflux
(GOR), (B) non-acid GOR, and (C) acid GOR during abdominothoracic straining. In (A) and (B), TLOSR (indicated by the horizontal black line)
triggers a common cavity (cc) episode the onset of which is closely associated with the onset of the pH change (vertical dotted line). In (C),
abdominothoracic straining (hatched bar) causes a sustained (>10 seconds) increase in intraluminal pressure across all channels. If LOS and
gastric pressure recordings are superimposed (see insert), the occurrence of a TLOSR at the end of the straining episode can easily be identified
by a prolonged equalisation LOS and gastric pressures (horizontal black line) which is associated with the onset of the GOR episode (vertical
dotted line).
Gastric half emptying time was measured with the buffering effect of saliva (fig 1B). Recognition of a common cavity episode with either no pH drop or even a pH increase which occurred within ±2 seconds of the onset of the common cavity was an essential additional requirement. Non-acid GOR episodes were identified by the presence of a common cavity episode with either no pH drop or even a pH increase which occurred within ±2 seconds of the onset of the common cavity and were not associated (±5 seconds) with the buffering effect of saliva (fig 1B).

Measurement of GE rate
Gastric half emptying time was measured with the 13C-octanoic acid breath test. 13C-labelled octanoic acid (50 µl) was added to the infant's regular feed and breath samples were taken as previously described.21 Breath samples were analysed for 13CO₂ content using an isotope ratio mass spectrometer. 13CO₂ excretion rate was used to calculate half GE time using the established non-linear regression model.13

Statistical analysis
Normally distributed group data were compared with an ANOVA technique (F test and/or Scheffe's test). Non-parametric grouped data were compared using the Mann-Whitney test. Interrelationships between variables were determined by Spearman-Rank correlation. Proportionate data were compared by χ² test. A p value <0.05 was considered statistically significant.

Associations between random variables (for example, TLOSRs and abdominal straining) were determined by calculating the 95% confidence intervals (CI) of the odds ratio. If CI was greater than 1 or less than −1, a significant association between variables was indicated.

RESULTS
Evaluation of patient symptoms, pH monitoring, and follow up
Infants assessed clinically to have GORD were older post-natally than normals (45 (8) v 25 (5) days old, respectively; p<0.05) and were more likely to be receiving xanthine therapy (71% v 38% on xanthines; p<0.01). No other significant age, size, or feeding differences (type, volume) were observed between the groups. Numbers of infants receiving two, three, and four hourly feeds were 4 (29%), 3 (21%), and 7 (50%), respectively, for the GORD group and 3 (14%), 7 (32%), and 12 (54%), respectively, for normals (NS). Adequate symptomatic assessment charting was completed in 19 normals and 12 patients with GORD. Analysis of the reflux symptom assessment charts confirmed more frequent symptoms overall in the GORD group; apnoea, choking, and behavioural changes in particular (fig 2). Infants in the GORD group had a median reflux index of 15.1% (interquartile range 9.8–30.0%), 10 infants (72%) had a reflux index of >10%, 3 (21%) had a reflux index of 5–10%, and one had a reflux index <5%. Median reflux indexes for two, three, and four hourly fed infants with GORD were 8.7%, 17.4%, and 41.4% respectively (p<0.01).

The follow up reflux questionnaire performed at three months after discharge was completed for 21 normals and 10 infants in the GORD group. Of the normals, 17 (81%) continued to be reflux free while eight (80%) of the infants in the GORD group continued to be symptomatic.

TLOSRs and GOR
TLOSR was the predominant mechanism of GOR triggering, accounting for 50–100% (median 91.5%) of all GOR episodes in the 36 patients. In all, 726 TLOSRs were recorded; of these, 105 (14%) were associated with acid GORD. Two hundred and sixty five (37%) TLOSRs were associated with non-acid GORD and 356 (49%) did not result in GORD, as defined by our criteria. Abdominal straining occurred commonly (average 41 (2) strains/study, range 13–64). Of all of the TLOSRs observed, 315 (43%) occurred during abdominothoracic straining with 71 associated with acid GORD. When a TLOSR occurred during abdominothoracic straining, acid GORD was more likely to occur than when a TLOSR was not associated with straining (odds ratio 4.32 (2.71, 6.88); p<0.001).

The occurrence of TLOSRs and the relationship between TLOSR and acid or non-acid GORD was significantly influenced by the time interval between feeds (two, three, or four hourly) (fig 3A–C). In infants fed four hourly (that is, fed only once immediately prior to the commencement of the four hour manometric study) the number of TLOSRs peaked in the first hour (fig 3A). In contrast, infants fed two hourly or three hourly (that is, fed on two occasions immediately prior to the study and then two or three hours into the study), a second peak in the number of TLOSRs was observed which corresponded to the one hour period immediately following the second feed (fig 3B, C). Feeding therefore changed the pattern of occurrence of TLOSRs and acid/non-acid GORD during the period 2–4 hours postprandially. Because of this, further comparisons among patients were limited to an analysis of events occurring during the period from initial feed to two hours postprandially. During this period the overall number of TLOSRs and TLOSRs associated with GORD were not significantly altered by feed frequency (9.1 (2.1), 9.0 (0.8), and 12.5 (1.9) for two, three, and four hourly feeds, respectively).

Feed type did not alter the rate of occurrence of TLOSRs (8.8 (0.8) v 11.6 (1.6) for EBM v formula, respectively; p=0.1) but EBM fed infants did have more acid GORD (13.3% v 7.0% for EBM v formula, respectively; p<0.05) and less non-acid GORD (32.2% v 43.5% for EBM v formula, respectively; p<0.05) in association with TLOSRs. Xanthine therapy did not significantly alter the number of TLOSRs (10.3 (1.2) ± 9.6 (1.2) for xanthine therapy v no therapy, respectively) or their association with acid GORD (11.9% v 9.0% for xanthine therapy v no therapy).
episodes, respectively. Infants with GORD had similar occurrence of all transient lower oesophageal sphincter
studies.

Figure 3 Occurrence of all transient lower oesophageal sphincter
relaxations (TLOSR) (lines) and TLOSRs associated with non-acid
gastro-oesophageal reflux (GOR) (light shading) and acid GOR (dark shading) in infants receiving feeds at (A) four hourly, (B) three
hourly, and (c) two hourly intervals. Data represent the mean number
of events recorded during each one hour period of the four hour
periods, with longer intervals between feeds being associated
with lower GE (25 (5) minutes, 30 (4) minutes, and 46 (5) minutes for two, three, and four hourly feeds, respectively;
p<0.05). This effect was most likely due to differences in feed
volumes administered which varied from 20 to 80 ml and were
lower in the more frequently fed infants (22 (1) ml, 43 (2) ml,
and 69 (3) ml in two, three, and four hourly fed, respectively;
p<0.0001). Xanthine therapy did not alter GE rate (33 (4) v 33
(5) minutes for xanthine therapy v no therapy respectively).
Infants with GORD had similar half GE times to normals (32
(7) v 33 (3) minutes, respectively).

DISCUSSION

This is the first study to characterise oesophagogastric motor
function and mechanisms of GOR in preterm and term
infants with GORD. While TLOSR was the predominant
mechanism of GOR in infants with GORD, the number of
TLOSRs was similar to normal infants but GORD infants had
a higher proportion associated with acid reflux. These data
demonstrate that TLOSR is likely to be a major contributing
factor to the pathophysiology of GORD in these babies.

Gastric distension (by feeding) stimulated TLOSRs with the
frequency of feeding altering the pattern of TLOSRs and the
relationship between TLOSRs and acid or non-acid GOR. This
affect was most evident during the period from two to four
hours postprandially and consequently differences seen
between infants with GORD and normals were less apparent
during this period due to the variability introduced because
some infants were fed during this period. Abdominal straining
was also an important factor increasing the likelihood of
TLOSRs to trigger acid GOR episodes.

Early studies in supine adult reflux patients indicated that
GORD was characterised by a higher number of TLOSRs trig-
gered in response to a meal, whereas infants with GORD
had a greater proportion of TLOSRs associated with acid GORD,
particularly during straining. Similar observations have now
been reported in adults with GORD and indicate that the
differences between normals and patients with GORD may be
due to sensory or anatomical variations that increase the like-
lihood for liquid (rather than gas) reflux to occur during
TLOSR.

Our data clearly show that GE was not delayed in GORD
patients and challenge the logic of acceleration of GE for the
treatment of acid reflux. The GORD patients studied did not
have significantly more regurgitation than normals, and
therefore we are unable to comment on gastric acceleration for
the treatment of infants with volume reflux. GORD patients
were more likely to be receiving xanthine therapy but
xanthines on their own did not appear to alter TLOSRs, GOR
triggering by TLOSRs, or GE rate.

In a study such as this, patient selection and grouping is
made difficult by the absence of “gold standard” diagnostic
criteria specific to this age group in which endoscopy is
usually unavailable or inappropriate. “Normal” oesophageal
pH monitoring scores have not been adequately defined in
infants, particularly premature infants. Most pH monitoring
therapy, respectively) and non-acid GOR (41.0 v 33.5% for
xanthine therapy v no therapy, respectively). The rate of
occurrence of TLOSRs was not affected by postmenstrual age
but there was a weak correlation between postnatal age and the
time of TLOSRs, with older infants having fewer TLOSRs
(r=0.32, p<0.05).

TLOSR was the predominant mechanism of GOR in both
normals and infants with GORD, being associated with 94%
(range 70–100%) and 92% (range 50–100%) of all GOR
episodes, respectively. Infants with GORD had similar
numbers of TLOSRs to normals (9.5 (1.2) v 10.4 (1.1), respecti-
vely from 0–2 hours, 6.9 (1.0) v 9.7 (1.1), respectively, from
2–4 hours postprandially) but had a significantly higher
number and proportion of TLOSRs associated with acid GOR
(1.6 (0.4) v 0.6 (0.1) (p<0.05) and 16.5% v 5.9% (p<0.0001),
respectively, from 0–2 hours; 1.7 (0.6) v 1.9 (0.4) (NS) and
25.0% v 19.7% (NS), respectively, from 2–4 hours postprandial-
ally). In contrast, the number and proportion of TLOSRs asso-
ciated with non-acid GOR were similar (4.0 (0.9) v 3.7 (0.6)
(NS) and 42.1% v 35.8% (NS), respectively, from 0–2 hours; 2.2
(0.5) v 3.5 (0.7) (NS) and 32.3% v 36.6% (NS), respectively,
from 2–4 hours postprandially). Straining in association with
TLOSR augmented the likelihood of acid GOR in both normals
(odds ratio 2.26 (1.54, 3.31); p<0.0001) and GORD (odds ratio
2.39 (1.36, 4.21); p<0.0001).

Gastric emptying

For all infants, mean half GE time was 33 (1) minutes, and
EBM fed infants had faster GE rates (28 (3) v 41 (6) minutes
for EBM v formula, respectively; p<0.05). Infants receiving
feeds at two, three, or four hourly intervals had different GE
times, with longer intervals between feeds being associated
with slower GE (25 (5) minutes, 30 (4) minutes, and 46 (5)
minutes for two, three, and four hourly feeds, respectively;
p<0.05). This effect was most likely due to differences in feed
volumes administered which varied from 20 to 80 ml and were
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studies have indicated that acid GOR is a common event; reflux index scores are much higher than levels considered clinically significant in adults and children. Furthermore, reflux parameters are altered by changes in arousal state, feed type, and posture. The disease status of the patients enrolled in this study was judged firstly on the basis of clinical assessment by a neonatologist and then further examined by reflux symptom charting and 24 hour oesophageal pH monitoring. Confirmation of the clinical diagnosis of GORD using pH monitoring has been used in other studies, indicating that infants selected in this way have increased acid oropharyngeal aspirations which may in itself be useful diagnostically.

Our confirmatory studies showed that infants in the GORD group had more frequent symptoms than normals and most had pathological GOR on pH monitoring. These were the best criteria we could apply to a very challenging patient group in whom demonstration of unequivocal GORD is often difficult. More frequent feeding had a marked effect in reducing the reflux index in this group of infants characterised by very high oesophageal acid exposure times. The effect of feeding frequency on the reflux index is entirely predictable based on the known effect of feeding on intra gastric pH and supports the clinical utility of the conservative option of decreased volume/more frequent feeding to treat mild reflux. Despite frequent feeding however all but one infant in the GORD group exhibited reflux indices that were greater than 5% and the three month follow up using an established reflux questionnaire indicated that 80% of these patients continued to exhibit significant symptoms three months after being enrolled in this study.

In conclusion, like older children and adults, TLOSR is an important factor in the pathophysiology of GORD in preterm and term infants while delayed GE does not appear to be. Further investigations are now needed to characterise intragastric pH in these babies.

ACKNOWLEDGEMENTS

This work was supported by grants from the National Health and Medical Research Council of Australia, the WCH Research Foundation, and the JH & JD Gunn Medical Research Foundation. Dr Benninga was supported by the Ter Meulen Fund, Royal Netherlands Academy of Arts and Sciences, the Netherlands Organisation for Scientific Research, and the Netherlands Digestive Diseases Foundation. We would like to thank Mr Malcolm Bakewell for invaluable technical support and Dr Charles Malbert for the computerised data acquisition and analysis software used.

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REFERENCES


