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Characterisation of relaxation of the lower oesophageal sphincter in healthy premature infants

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Abstract

Background—**Gastro-oesophageal reflux disease causes significant morbidity in premature infants, but the role of dysfunction of the lower oesophageal sphincter (LOS) in this condition is unclear.**

Methods—**Oesophageal manometry was performed after gavage feeding in 13 healthy preterm neonates (postmenstrual age ≥33 weeks) with a perfused sleeve with side hole assembly. Swallow related (both single and multiple) and transient LOS relaxations (TLOSRs) were identified and the characteristics of these events defined. Reflux was identified with manometric criteria (common cavity episodes).**

Results—**Five hundred and eleven relaxations of the LOS were observed, 55% related to single swallows, 23% related to multiple swallows, and 22% TLOSRs. The time to maximal LOS relaxation was longer for TLOSRs than for single or multiple swallows (mean (SEM) 5·0 (0·3) s *v* 3·0 (0·1) s and 3·3 (0·1) s, p<0·0001 and p<0·005). The durations of multiple swallows and TLOSRs were longer than single swallows (12·2 (0·5) s and 11·2 (0·4) s *v* 5·3 (0·2) s, p<0·0001). Most of the oesophageal body common cavity episodes (94%) occurred during TLOSRs.**

Conclusions—**In healthy preterm infants (postmenstrual age ≥33 weeks) the motor events associated with LOS relaxation were similar to those seen in healthy adults. TLOSRs may be an important mechanism of reflux in premature infants.**

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Keywords: preterm noenate, oesophageal motility, lower oesophageal sphincter relaxation, transient lower oesophageal sphincter relaxation, gastro-oesophageal reflux, common cavity.

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Gastro-oesophageal reflux disease is a significant cause of morbidity in infants and may manifest as frequent vomiting, with or without failure to thrive, and complications such as oesophagitis, apnoea, bradycardia, aspiration pneumonia, and chronic lung disease. There is also of an association between gastro-oesophageal reflux and sudden infant death syndrome.[1]

The tonic pressure at the gastro-oesophageal junction generated by the lower oesophageal sphincter (LOS) is the major barrier to reflux of gastric contents into the oesophagus. Monitoring of LOS pressures with a sleeve sensor,[2] in conjunction with simultaneous pH recording, has shown that oesophageal acidification in adults and children is more often associated with TLOSRs than with low resting LOS tone.[3–8] The mechanisms of gastro-oesophageal reflux in prematurity remain unclear. Previous studies of LOS function in premature neonates determined the resting LOS pressure at the gastro-oesophageal junction with a pull through technique. Pressure at the LOS was reported either to be low (0–6 mm Hg)[9–11] or to increase towards term.[12] It is now recognised that measurement of LOS pressure by a pull through technique does not provide an accurate recording of the fluctuations of LOS pressure over time[4 5 8] and does not reliably evaluate LOS relaxation.[13 14] Furthermore, manipulation of the manometric assembly during a pull through technique may itself cause substantial physiological disturbance.

The relative lack of data on motor function of the LOS in premature neonates prompted the development of perfused manometric assemblies incorporating sleeve sensors, that were suitably sized for studies in premature infants (2·0 mm ouside diameter). A study using this method[15] showed that mean LOS pressure of premature infants was 13–26 mm Hg. These pressures are within the range usually associated with competence of the oesophago-gastric barrier (>5 mm Hg). In addition the mean resting LOS pressure fluctuated substantially over time and was decreased significantly in response to feeding in a similar fashion to that seen in older subjects.[4 5 8] The aims of the current study were to identify and characterise motor events associated with LOS relaxation in healthy premature infants and to determine the oesophageal and LOS motor mechanisms responsible for gastro-oesophageal reflux episodes identified manometrically as common cavities.

Methods

Subjects

Twenty eight studies were performed on 13 healthy preterm infants (eight male; five female). The babies had a mean gestational age of 32 (range 28–36) weeks, mean postnatal age of 37 (range 5–83) days, and mean postmenstrual age (mean gestational age+mean postmenstrual age) of 35·7 (range 33–40) weeks. Gestational age was determined from both maternal history of due dates and ultrasonic intrauterine morphometric assessment.

When there was a discrepancy between maternal history and ultrasound assessment, gestational age was determined by examination of the anterior vascular capsule of the eye lens.[16] Body weight and feeding history were also recorded. Infants receiving theophylline or caffeine (12 studies) were not excluded due to the frequent use of these agents for treatment of apnoea or bradycardia, or both. All infants were undergoing routine gavage feeding with non-fortified expressed breast milk (17 studies) or infant formula (Enfalac 20/24 calorie, Mead Johnson, Canada; 11 studies).

The study protocol was approved by the ethics research committee of the Women's and Children's Hospital in 1994 and written informed parental consent was obtained before each study.

Recording technique

The manometric approach used in this study permitted monitoring of pressures, at very low rates of manometric infusion, with an assembly that could also be used to feed the infants.[15] In addition, the manometric lines and assembly were designed so that they could be sterilised by autoclaving to remove possible infection hazards. The requirements of the micromanometric perfusion system for use in preterm infants and the dynamic performance characteristics of the catheter have been previously described and validated.[15 17]

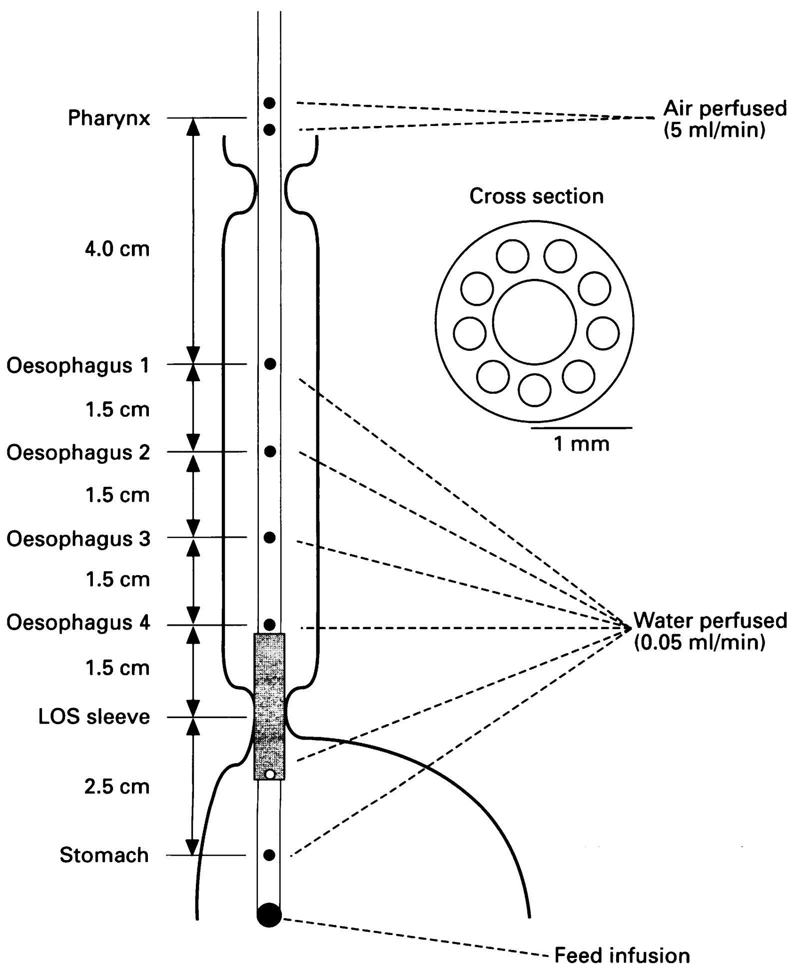

Figure 1: Arrangement of side hole sensors for the assembly and position within the oesophagus. Included is a cross section of the 10 lumen (nine manometric channels 0·35 mm inside diameter + one feeding channel 0·75 mm inside diameter) microextrusion used in the construction of the assembly.

A purpose built silicone rubber manometric microassembly was constructed from a multilumen microextrusion (2 mm outside diameter) which had nine recording lumina (0·35 mm inside diameter) arranged around a larger feeding channel. Perfusion rates were accurately regulated with purpose built hydraulic resistors made of individually calibrated lengths of stainless steel tube (0·1 mm internal diameter/1·5 mm outside diameter) to deliver a flow rate of 0·05 ml/min water or 5 ml/min air at a fixed driving pressure of 400 mm Hg. As bubble entrapment substantially impairs rates of pressure rise at low infusion rates, complete removal of bubbles from the assembly and perfusion system, including the water reservoir, was achieved by flushing the system with CO_2 before filling with sterile degassed distilled water. Any CO_2 bubbles still retained in the system after filling with water dissolved into the perfusate.

The assembly incorporated a 2·5 cm long sleeve sensor. The performance of the miniature sleeve sensor was validated with a miniaturised version of a sphincter model.[17] Bench top testing[2] showed uniformly accurate detection of pressure along its length. The pressure rise rate on occlusion of the sleeve at a perfusion rate of 0·05 ml/min ranged from 11·0 (0·1) mm Hg/s 2·5 cm from the sleeve perfusion side hole to 55·7 (SEM 0·8) mm Hg/s just beyond the point of entry of perfusate into the sleeve. The sensor was perfused retrogradely, (from the gastric end of the sleeve) to ensure that cephalad movement of the LOS relative to the sleeve would be towards the sleeve perfusion side hole. This provides a more accurate measure of extrinsic crural diaphragm compression of the LOS segment than a conventionally perfused sleeve.[18]

Side holes positioned along the extrusion recorded pressures from the pharynx (two), oesophageal body (four), LOS (sleeve), and stomach (one) (Figure 1). Pharyngeal side holes used to monitor swallowing were air perfused (5 ml/min) to allow reliable monitoring of pharyngeal pressure waves without water infusion. Oesophageal, sleeve and gastric side holes were perfused with sterile degassed H_2O.

Analogue pressure transducer signals were amplified and filtered with a Synectics polygraph (Synectics, Stockholm, Sweden) and digitised at 10 Hz using an A-D card (National Instruments, Austin, TX, USA). Data acquisition and analysis were performed on a Macintosh Quadra 700 with software based on National Instruments' Labview (MAD software, Royal Adelaide Hospital, C Malbert, Australia).

Protocol

The assembly was passed transnasally and positioned with the sleeve straddling the LOS high pressure zone of the gastro-oesophageal junction and the two air perfused side holes in the pharynx (Fig 1). The nares-LOS distance of the infants studied ranged from 14 to 18 cm. After positioning the assembly, the manometric perfusion was not started until the feed was given via the assembly core channel. Feed volumes ranging from 30 to 95 ml were given manually with a syringe over 15–35 minutes. After the feed, manometric infusion was restarted and spontaneous oesophageal body and LOS motor patterns were recorded for two hours.

Mean total daily feed volume was 172·6 (SD 3·4) ml/kg/day (range 140–225 ml/kg/day). To compensate for the volume of the manometric perfusate the feed volume during the studies was reduced by 20%–35%. When all manometric side holes were perfused, the total volume of distilled water infused by the assembly during the study was 36 ml (18 ml/hr). This volume was infused in 15 studies. During studies of smaller infants (≤2000 g), the volume was reduced to 30 ml (eight studies) or 24 ml (five studies) by not perfusing one or two of the most proximal oesophageal body side holes. In all cases the extra fluid infusion increased the total fluid volume given during a 24 hour period by <10%.

Analysis of manometric recordings

Relaxation of LOS – For each recording period sleeve recorded LOS relaxations were identified and analysed. Only those preceded by a stable baseline pressure for ≥3 seconds before the onset of relaxation and free from strain induced pressures (sustained increases in gastric and oesophageal pressure ≥5 mm Hg for ≥5 s) were analysed. Relaxations of the LOS were classified as (*a*) single swallow related relaxations, when a single swallow occurred within ±5 s of the onset of relaxation; (*b*) multiple swallow related relaxations: a sequence of two or more swallows occurring during a relaxation, with the first swallow occurring within ±5 s of the onset of relaxation; or (*c*) transient relaxations: swallowing was absent for five seconds before and after the onset of relaxation. The onset of swallowing was defined by the onset of the upstroke of the hypopharyngeal pressure wave. Figure 2 shows examples of the three types of LOS relaxation. Each relaxation was analysed with established criteria[7] for: (*a*) *resting pressure* – tonic end expiratory LOS pressure immediately before relaxation; (*b*) *nadir pressure* – minimum LOS pressure attained during relaxation; (*c*) *time to maximal relaxation* – time from onset to maximal relaxation; (*d*) *duration of relaxation* – time during which LOS pressure was ≤20% of the resting nadir pressure difference (for example, if resting pressure is 10 mm Hg and nadir pressure is 0 mm Hg, the duration is the time for which LOS pressure is ≤2 mm Hg). Pressure of the LOS was defined as the difference between end expiratory sleeve pressure and gastric pressure.

Manometric indicators of reflux – Common cavity episodes were used as manometric indicators of the flow of liquid or gas from the stomach into the oesophagus.[19] In adults, common cavities commonly accompany episodes of acid reflux but they also occur in association with small fluctuations in pH. These small fluctuations are presumably due to reflux of small quantities of acid, flowing in association with larger volumes of gas.[5] A common cavity episode was defined as an abrupt, sustained increase in intraoesophageal pressure to gastric pressure that occurred in the absence of a comparable change in intragastric pressure (strain). The magnitude of the increase in intraoesophageal pressure and the duration of the common cavity in the two to three most distal oesophageal channels were analysed and the mean taken. Depending on the hypopharyngeal pressure recordings, oesophageal body contractions found during common cavity episodes were classified as being primary (swallow associated) or secondary (independent of swallowing). The pressure wave sequence of the contractions was characterised as *peristaltic* if the propagation velocity was ≤3 cm/s, and *synchronous* if it was either >3 cm/s or simultaneous on two or more channels.

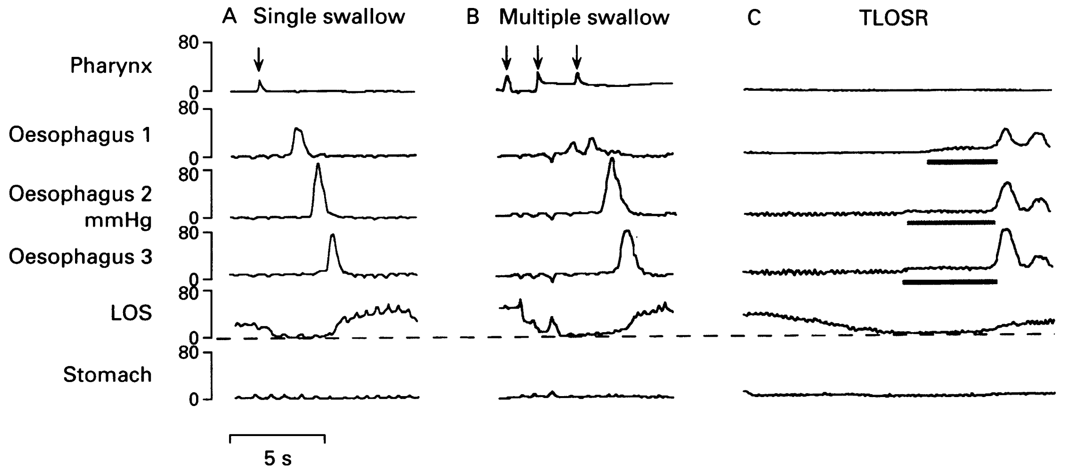

Figure 2: Example of pharyngeal, oesophageal, and LOS pressure tracings in premature infants showing three types of LOS relaxation: (a) single swallow; (b) multiple swallows (sequence of three s); (c) transient LOS relaxation with a common cavity episode (black bar) followed by an oesophageal body contraction seen in all oesophageal body channels. Arrows indicate swallows.

Statistical analysis
Data are means (SEM) unless otherwise stated. Grouped data of different sample size were compared with an *F* test and Scheffe's test and the proportions of pressure wave types observed in association with common cavities were compared using a Fisher-Irwin exact test.

Results

The combined manometric/feeding assembly was well tolerated by all infants and no adverse effects were noted. Mean infant weight was 2192 (range 1420–2860) g.

Characteristics of LOS relaxation
Five hundred and eleven separate LOS relaxations were analysed; 282 (55%) related to a single swallow and 115 (23%) to multiple swallow episodes. A further 114 relaxations (22%) did not occur within ±5 s of the onset of a swallow signal and were classified as TLOSRs. TLOSRs were observed in all studies with a mean of 2·3 (0·3) (range 0·5–6)/hr.

The mean onset time of single swallow related LOS relaxations was 0·5 (0·1) s after pharyngeal contraction, 88% of these occurred within the normal adult range of between two seconds before and four seconds after onset of the hypopharyngeal pressure wave.[7] During LOS relaxations associated with multiple swallows, the mean number of pharyngeal contractions was three (range two to six).

Mean resting pressures recorded at the onset of relaxation were similar for all types of LOS relaxation (Table I). Neither feed type (EBM/formula) nor treatment with theophylline altered the mean resting pressure (p>0·08 and p>0·9 respectively). The mean nadir pressures recorded for single swallows did not differ significantly from the nadirs of multiple swallows and TLOSRs (Table I). The time to maximal relaxation was significantly longer for TLOSRs than for single and multiple swallows (Table I). The duration of relaxation during TLOSRs and multiple swallow LOS relaxations was similar and significantly longer than for single swallow LOS relaxations (Table I). There was a weak positive correlation between duration of LOS relaxation and the number of pharyngeal contractions during multiple swallows (r=0·35, p<0·0005).

TABLE I *Characteristics of single and multiple swallow related LOS relaxations and transient LOS relaxations (TLOSRs) in premature infants*

LOS relaxation characteristics	*Type of LOS relaxation* Single swallow (n=282)	Multiple swallow (n=115)	TLOSR (n=114)
Resting LOS presssure (mm Hg)	24·9 (0·7) (3·0 to 56·0)	23·4 (1·1) (5·0 to 56·0)	27·0 (1·2) (4·0 to 73·0)
Time from swallow to relaxation onset (s)	0·5 (0·1) (–4·9 to +4·7)	—	—
Time from onset to maximal relaxation (s)	3·0 (0·1)‡‡ (0·5 to 9·7)	3·3 (0·2)‡ (0·9 to 13·0)	5·0 (0·3)**† (0·7 to 20·7)
Nadir LOS pressure (mm Hg)	2·5 (0·2) (0·0 to 22·0)	1·8 (0·4) (0·0 to 29·0)	2·0 (0·4) (0·0 to 28·0)
Duration of relaxation (s)	5·3 (0·2)†‡ (0·7 to 16·4)	11·2 (0·4)* (3·2 to 30·0)	12·2 (0·5)* (3·0 to 27·2)

Data are expressed as mean (SEM) (range).
*p<0·001; **p<0·0001 *v* single swallow.
†p<0·001 *v* multiple swallow.
‡p<0·001; ‡‡p<0·0001 *v* TLOSR.

TABLE II *Characteristics of transient LOS relaxations (TLOSRs) associated with common cavity episodes and other TLOSRs in premature infants*

TLOSR characteristics	*Common cavity (n=32)*	*No common cavity (n=82)*
Resting LOS pressure (mm Hg)	25·3 (2·8) (4·0 to 73·0)	27·7 (1·3) (7·0 to 58·0)
Time from onset to maximal relaxation (s)	5·4 (0·6) (0·7 to 13·6)	4·8 (0·3) (1·2 to 20·7)
Nadir LOS pressure (mm Hg)	0·4 (0·2)* (0·0 to 5·0)	2·6 (0·5) (0·0 to 28·0)
Duration of relaxation (s)	15·9 (0·9)** (6·5 to 27·2)	10·7 (0·5) (3·1 to 25·6)

Data are expressed as mean (SEM) (range).
*p<0·01; **p<0·0001.

Common cavity episodes
Thirty four common cavity episodes were recorded, 32 associated with TLOSRs and two with multiple swallowing. The mean duration of the common cavity events was 12·1 (1·3) s (range 2·8–35·6) s with a mean increase in resting oesophageal body pressure of 4·0 (0·4) (range 1–12) mm Hg. Common cavities occurred at a mean frequency of 0·6/hour. Neither feed type (EBM/formula) nor treatment with theophylline altered the frequency of common cavities (p>0·8 and p>0·2 respectively).

Twenty eight per cent of TLOSRs were associated with common cavity episodes. Basal pressures before relaxation and the time taken for relaxation to occur were similar for TLOSRs associated with common cavities and other TLOSRs (Table II). Nadir pressures were significantly lower and the durations of relaxation were significantly longer for TLOSRs associated with common cavities (Table II).

Oesophageal body pressure waves occurred during all common cavity episodes, 59·5% being secondary pressure waves and 40·5% primary pressure waves. A significantly higher proportion of secondary pressure waves were synchronous in sequence when compared with primary pressure waves, which were predominantly peristaltic and rarely synchronous (42·1% *v* 14·2% (single swallows) and 16·7% (multiple swallows) respectively, p<0·001).

Discussion

In this study a sleeve sensor was used to examine the motor events associated with LOS relaxation and gastro-oesophageal reflux in healthy premature infants for two hours after feeding. Consistent with our recent studies[15] mean resting LOS pressure at the onset of relaxation was greater than 20 mm Hg. These data conflict with earlier findings of low LOS pressures in premature babies in which a pull through technique was used to measure LOS pressure.[9–11] Mechanical stimulation of the pharynx, such as occurs with catheter movement, may inhibit LOS contractions either directly or by stimulating swallowing.[20] It is also well recognised that there is considerable variation in resting LOS pressure reflecting the phase of the interdigestive migrating motor complex, cyclical hormonal release, and changes in arousal state.[4 5 8] The pull through technique is, however, unable to record accurately the temporal fluctuations in resting LOS pressures for prolonged periods. It therefore seems likely that the studies performed with the pull through technique may have underestimated LOS pressure.

Safe reliable monitoring of hypopharyngeal pressures was essential for accurate timing of the onset of LOS relaxations in relation to deglutition. Non-perfused side holes lack the necessary fidelity to record accurately from the hypopharynx. Although water perfused side holes can be used to monitor pressures in this region, this approach is inappropriate in premature infants because of the risk of aspiration. Furthermore, pharyngeal perfusion with water may inhibit LOS pressure and cholinergic pathways regulating peristalsis.[20 21] We therefore chose to monitor swallowing using air perfusion of two radially opposed side holes in the hypopharynx. Channels perfused using this technique had a rise rate of >100 mm Hg/s which is sufficient to provide a swallow signal. In addition, air perfusion did not stimulate swallowing and reduced the perfusate load during the studies.

In this study, resting LOS pressure, and the relation between swallowing and LOS relaxation, time to maximal relaxation, and duration of LOS relaxation were similar to those previously reported in healthy adults.[7] These similarities were present even though our study examined spontaneous dry swallows, whereas in the adults the LOS response to voluntary dry and wet swallows was studied. We therefore used a broad time window to ensure that all swallow related relaxations were included. Although this may have resulted in the classification of some TLOSRs as swallow related, it did not have a significant impact on the major differences in the characteristics of LOS relaxations between the two groups. The similarities between the data for adults and ours suggest that the integrative mechanisms required to coordinate LOS inhibition and swallowing are already present by 33 weeks postmenstrual age. TLOSRs, which are thought to be vagally mediated, were also frequent during our study indicating that the neural pathways responsible for transient inhibition of LOS tone in the absence of swallowing also develop by 33 weeks. These findings are in keeping with those from other regions of the upper gastrointestinal tract such as the stomach and small intestine, in which motility patterns also seem to be well developed by 32–34 weeks.[22–24] It is also of interest that although primary contractions were almost exclusively peristaltic after reflux events, more than 40% of secondary contractions were synchronous suggesting that the mechanisms which underlie secondary peristalsis are less well developed. These findings are in keeping with our previous report that most oesophageal body contractions occurring independently of swallowing are non-peristaltic.[15] As synchronous oesophageal contractions do not clear luminal contents efficiently[25] they may prolong oesophageal acid exposure contributing to mucosal injury.

The absence of an oesophageal pH sensor in the current study limits the interpretation of motor events in relation to acid reflux. However, one third of TLOSRs were associated with common cavities – episodes of oesophageal body pressurisation to gastric pressure by liquid or gas reflux. In older children with gastro-oesophageal reflux disease, common cavity episodes are seen in 79% of acid reflux episodes (H Kawahara, personal communication). TLOSRs associated with common cavities in the current study had similar nadir pressures and durations to those associated with reflux episodes determined by pH-metry in adults. By contrast, relaxation was less complete and of shorter duration in TLOSRs which were unassociated with common cavities.

It is possible that we may have underestimated the number of gastro-oesophageal reflux episodes triggered either during abdominal straining or by other mechanisms which do not allow common cavities to be identified. The close association between common cavity episodes and TLOSRs on the background of well sustained LOS pressure suggests that TLOSRs are an important mechanism for gastro-oesophageal reflux in healthy preterm infants.

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