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Temporal Association Between Reflux-like Behaviors and Gastroesophageal Reflux in Preterm and Term Infants

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Abstract

Objectives—Multichannel intraluminal impedance studies (MII-pH) have become the criterion standard for the diagnosis of gastroesophageal reflux (GER). Several clinical signs and symptoms that are attributed to GER during infancy may not be related to true reflux. Our objective was to correlate the observed reflux-like behaviors to reflux events on MII-pH studies.

Methods—This is a retrospective study on infants being evaluated for GER with MII. During the MII-pH study, the infants were observed for clinical behaviors. Symptom Index (SI), symptom sensitivity index (SSI), and symptom association probability were used to correlate symptoms with reflux events.

Results—Of 58 infants (40 preterm, 18 term) included in the study, only 6 infants (10%) had an abnormal MII-pH study. Irritability (32 infants), bradycardia (20), and desaturation (18) were the common signs and symptoms. A total of 2142 (755 acidic and 1386 nonacidic) reflux episodes and 953 clinical reflux behaviors were recorded. The incidence and pattern of GER was similar in preterm and term infants. There was no significant difference in GER episodes and acid exposure in preterm infants fed orally or via nasogastric tube. The symptom association probability was abnormal in only 6 (19%), 1 (5%), and 5 (28%) infants with irritability, bradycardia, and desaturation, respectively.

Conclusions—The prevalence of GER as detected by MII-pH was low (10%) in symptomatic preterm and term infants. The incidence and pattern of GER was similar in preterm and term infants. The majority of suspected clinical reflux behaviors did not correlate with reflux events.

Keywords

gastroesophageal reflux disease; multichannel intraluminal impedance; neonates; symptom association

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Gastroesophageal reflux (GER) is defined as the involuntary passage of gastric and duodenal contents into the esophagus. When GER causes significant signs and symptoms, it is called gastroesophageal reflux disease (GERD). The prevalence of GERD in children ranges between 1.8% and 8.2%, and is more common during the first year of life (1). Extraesophageal manifestations, such as wheezing or pneumonia, can also occur in some infants and children with GER who aspirate gastric contents into the lungs (2). Although the pH probe study has historically been the criterion standard test to diagnose GERD in infants and children, it does not provide information about nonacidic reflux, which can be more common in preterm infants (3,4). The multichannel intraluminal impedance with pH probe (MII-pH) has been increasingly used in adults and children, and is now considered the criterion standard for the diagnosis of GERD in adults (5,6). The MII-pH study has advantages over a pH study because it not only detects both acidic and nonacidic refluxate, it can also differentiate antegrade (swallow) from retrograde (true GER) flow, measure the height of refluxate, determine whether refluxate is liquid, gas or mixed, and also assess symptom association. The MII-pH study can be used to detect reflux during most types of enteral feeding (ie, continuous nasogastric [NG], nasojejunal [NJ], bolus NG, and oral feeds) (4).

A variety of signs and symptoms during infancy have been attributed to GERD. These include persistent vomiting, irritability, arching, apnea, bradycardia, desaturation, cough, gagging, wheezing, apparent life-threatening events, feeding difficulties, and failure to thrive (1,7). Data correlating these signs and symptoms to actual GER events are sparse. Several investigators have correlated signs and symptoms of GER with the acidic events detected by a pH study (8–10). The pH study, however, does not provide information about nonacidic reflux (3,4). Only a few studies have used MII-pH to correlate clinical signs and symptoms of GER with GER episodes during infancy (11–15). These studies are small, short (duration <6 hours), or limited (correlating only with a few signs or symptoms with GER). Moreover, the data associating clinical signs and symptoms with actual GER events are conflicting. Our objective was to correlate observed reflux-like behaviors to true reflux events on MII-pH studies during infancy using a larger sample size and observing for a longer period. We hypothesized that several of the clinical signs and symptoms that are attributed to GER during infancy may not be related to true reflux events.

METHODS

Study Population

This study was a retrospective review of infants being evaluated for suspected GER between October 2009 and January 2012 using the MII-pH probe monitoring system. The study included both inpatients (n = 41) and infants from the outpatient (n = 17). They were referred for evaluation because of a high index of suspicion based on clinical symptoms. The patients were recruited from the neonatal intensive care unit (NICU) or the pediatric floor at the Thomas Jefferson University Hospital. The institutional review board of Thomas Jefferson University Hospital approved this study.

MII-pH Probe Monitoring

The infants were evaluated using the Sandhill Scientific Inc. (Highlands Ranch, CO), MII-pH probe equipment for a period of 16 to 24 hours. The infant catheters (Sandhill Scientific) with a diameter of 2.13 mm (6.4 French) and 7 impedance sensors (6 sensor spacing) were used. The length of the probe was estimated by measuring the distance between earlobe and tip of the nose then to xiphisternum. The position of pH probe was confirmed by chest x-ray and adjusted to a final position between T7 and T9. The impedance catheter was placed after 3 hours of fast. The pH sensor was calibrated before each analysis using a pH 4 and pH 7 buffer solutions. The top 3 clinical behaviors warranting the study were identified and recorded real time via push buttons during the impedance evaluation. As this study was performed on both an inpatient pediatric floor and the NICU, nursing staff was present 24 hours to observe and record specific clinical behaviors in the infants. Parents were also taught and encouraged to record symptoms throughout the study. Following completion of the study, the data were downloaded, reviewed, and analyzed by the pediatric gastroenterologists (S.A. or J.D.). The reflux characteristics for each patient along with the clinical behaviors were compiled. These data were further analyzed by the study team (A.F and Z.A.) to determine whether correlation between clinical signs/symptoms and reflux events existed as detected by the MII-pH probe. MII-pH reflux events were defined by a retrograde fall in impedance >50% from baseline in at least 2 distal channels. The event was then classified as acidic (pH < 4) or weakly acidic (pH > 4 and <7) based on pH data. The percentage of time the pH < 4 on the pH probe was called the reflux index. The number of episodes for each infant during the study period was recorded and number of events per hour was calculated. Clinical symptoms were considered as correlating if they occurred 5 minutes before or after a reflux event. Similar to other investigators, a generous time interval (5 minutes before and 5 minutes after) was used to maximize the correlation between symptoms and reflux episode (13,15,16). The Sandhill Scientific software package was used for symptom association analysis. The data were used to calculate the symptom index (SI = percentage of symptoms related to GER episode), the symptom sensitivity index (SSI = percentage of GER episodes associated with symptoms), and the symptom association probability (SAP). SAP is a statistical means (Fisher exact test) of calculating the probability that the symptoms and GER episodes are unrelated. The *P* value of this test is subtracted from 100% to reveal the SAP (17). These indices were considered positive when the SI>50%, SSI > 10%, and SAP > 95%. The normal values from premature infants, as well as adult studies were used for reference (3,18). In a study of 21 asymptomatic preterm neonates, Lopez-Alonso et al (3) reported the median number of reflux episodes in a 24 hours period was 71 (100, 95th percentile) and the median total acid exposure was 5.59% (20%, 95th percentile). Infants with a median number of episodes in a 24-hour period >100 (normalized to >75 in 18 hours period) or reflux index of >20% were considered as having an abnormal MII-pH study.

Statistical Analysis

Statistics were performed using the Sigma Stat 3.1 for Windows statistical package (Systat Software, Inc. Point Richmond CA). Data are expressed as a median with an interquartile range (IQR) unless specified otherwise. Comparisons between preterm and term groups and PO (per os) vs NG groups were performed using Student *t* test and Mann-Whitney rank-sum

test for continuous data, and Fisher exact test for categorical data. SAP, SI, and SSI were correlated by using Pearson correlation. Statistical significance was attributed to a *P* value <0.05.

RESULTS

Patient Demographic/Clinical characteristics

A total of 58 infants were included in the study, 18 term and 40 preterm (<37 weeks). A total of 17 infants were admitted from outpatient clinic for MII-pH study, whereas the remaining 41 infants were inpatients admitted in the NICU. The demographic and clinical characteristics are depicted in Table 1. The median age at the time of study was 70 days. Irritability was the most common (55% of infants) indication for MII-pH study (Fig. 1). Bradycardia (35%), desaturations (31%), and cough (21%) were the other major indications for study.

Analysis of MII-pH Data

A total of 2142 reflux episodes and 953 clinical reflux behaviors were recorded in 58 infants. The weakly acidic reflux episodes were more common (1386,64.7%) than acidic reflux (755, 35.3%). The median number of events per hour were 0.67 (acidic), 1.09 (weakly acidic), and 2.03 (total) (Table 2). Only 6 infants (10.3%) had acid exposure >20% or reflux episodes >4.2 per hour. There were no significant differences in the number of acidic, nonacidic, and total reflux events between preterm and term infants (Table 3). The number of infants with acid exposure >5% or >20% and the percent time of acid exposure (pH < 4) were similar amongst the 2 groups.

PO Versus NC feed and CER

A total of 20 preterm infants were on full oral (PO) feeds and 20 infants were receiving NG feeds at the time of study. There were no significant differences in the median number of acid reflux per hour (0.61 [0.37–1.17] vs 0.59 [0.10–1.28], $P = 0.75$), nonacid reflux (1.41 [0.97–1.76] vs 0.54 [0.22–0.80], $P = 0.08$) or total reflux (2.16 [1.57–2.63] vs 1.73 [0.76–2.36], $P = 0.21$) between infants who received PO versus NG feeds. The percent time of acid exposure was similar in infants fed PO versus NG (3.1 [1.82–6.35] vs 2.85 [0.00–5.92], $P = 0.97$).

Symptom Association Analysis

Table 4 and Figure 2 depict symptom association analysis expressed as SI, SSI, and SAP. Irritability was the most common indication for the study. A total of 372 episodes of irritability were recorded in 32 infants; however, a temporal relation between irritability and reflux events based on SAP existed in only 6 infants (19%). Similarly, 122 episodes of bradycardia were recorded in 20 infants, but a temporal relation with reflux events was seen in only 1 infant (5%). Gagging was significantly correlated with reflux events in 4 of 7 infants (57%).

Correlation Between SI, SSI, and SAP

SI, SSI, and SAP significantly correlated with each other ($P < 0.05$ between SI and SSI, $P < 0.001$ between SI and SAP, and $P < 0.01$ between SSI and SAP). The correlation, however, was strongest between SI and SAP ($r^2 = 0.64$).

Acid Suppression and MII-pH Data

A total of 10 infants (17%) were on acid suppression therapy (omeprazole = 5, 1 mg · kg^{-1} · day^{-1}; raniditine = 3, 6 mg · kg^{-1} · day^{-1}; lanzoprazole = 1, 1 mg · kg^{-1} · day^{-1}; and famotidine = 1, 1 mg · kg^{-1} · day^{-1}) during the MII-pH study and only 1 infant was on prokinetic therapy (metoclopramide, 0.3 mg · kg^{-1} · day^{-1}). The median percent of time pH<4 was significantly lower in infants on acid suppression therapy (0.6% vs 3.2%, $P = 0.04$). The median number of acid reflux was also lower in infants on acid suppression (7 vs 13, $P = 0.04$). The total number of reflux episodes were, however, similar (37 vs 40, $P = 0.4$) in the 2 groups, and the number of nonacidic reflux was significantly higher in infants on acid suppression (28 vs 17, $P = 0.046$). There were no significant differences in symptom association analysis in infants with and without acid suppression therapy (data not shown); however, the number of infants on acid suppression was too small for this comparison.

DISCUSSION

GER is common during infancy. A large number of signs and symptoms during infancy are attributed to GER. Our data indicate that in preterm and term infants where there is a strong clinical suspicion for reflux, the true prevalence of GERD is low. In these infants with a high index of suspicion, only 10% to 13% of them had true GERD as determined by MII-pH study. Moreover, the majority of clinical behaviors attributed to GER do not correlate with the reflux episodes.

Making a diagnosis of GER during infancy may be difficult. A pH probe study is the most commonly used tool to diagnose GER in infants and children. The pH study, however, does not provide information about nonacidic reflux (3,19). Other methods used to aid in the diagnosis of GER include an upper gastrointestinal barium study (to assess anatomy) and nuclear scans (to assess microaspiration). These methods are unreliable because of the short time period of observation, and have the additional disadvantage of exposure to radiation. Recently, the multichannel intraluminal impedance (MII) has been increasingly used in adults and children, and considered as the criterion standard for the diagnosis of GER (6,20). MII-pH study can detect both acidic and nonacidic refluxate. Several investigators have reported normal impedance values for adults (18,21). The data, however, are limited regarding normal range and baseline reflux characteristics using MII-pH study during infancy. Lopez-Alonso et al (3) reported MII-pH data on 21 asymptomatic preterm neonates. The median number of reflux episodes in a 24-hour period was 71 (100, 95th percentile), the median total acid exposure was 5.59% (20%, 95th percentile)(3). More recently, Mousa et al (22) reported reference values for impedance data from 117 infants and children. They found similar results of total reflux episodes for 24 hours during infancy (median 54, 95th percentile 93). In our study, we used data from Lopez-Alonso et al as the reference value because the populations were more similar. Only 6 infants (10.3%) in our cohort had an

abnormal MII-pH study defined as >95th percentile reflux episodes per hour or >95th percentile acid exposure time. Although we performed the MII-pH study in preterm and term infants in whom GERD was strongly suspected based on clinical symptoms, the prevalence of an abnormal MII-pH study was low.

Premature infants are more prone to GER because of immature tone of the lower esophageal sphincter, supine positioning, small stomach capacity, decreased esophageal capacitance, delayed gastric emptying, decreased gastrointestinal motility, and the presence of an NG tube (8,23,24). Premature infants are also less likely to have acidic reflux as gastric pH is >4, 90% of the time (3). We found no differences in the number of acidic, nonacidic, and total reflux events between preterm and term infants. Likewise, the percent time of acid exposure was similar between preterm and full-term infants. This is the first study to compare GER in preterm and term infants using MII-pH data. The finding of no differences in number and characteristics of the reflux episodes is likely because of selection bias as MII-pH studies were only performed in infants with a strong clinical concern for reflux. The majority of reflux events in preterm and term neonates were weakly acidic as described in previous reports (3,5). Therefore, MII-pH is a better study in infants to diagnose GERD, as the pH study will miss the majority of reflux episodes in this population.

It is commonly believed that an NG tube passing through the lower esophageal sphincter can trigger reflux episodes. The data, however, on the presence of NG tube and GER are conflicting (25,26). Dotson et al (26) reported that presence of NG tube did not cause reflux in healthy adults. In a small study on 16 neurologically impaired children (9 NG fed, 7 orally fed), there were no significant differences in total reflux events ($P = 0.628$) in NG fed versus orally fed children (27). There was, however, a trend ($P = 0.058$) toward higher nonacidic reflux events in NG fed children. In a study in term infants and children, a small size NG tube (8F) did not cause reflux, but GER was increased with a larger tube (12F) (28). Peter et al (29), reported data on 16 preterm infants who underwent a 48-hour MII study (24 hours with catheter tip in lower esophagus and 24 hours in stomach). The number of reflux episodes in 24 hours was significantly higher in gastric positioning of catheter versus esophageal placement (122 vs 72, $P<0.01$). We speculate that increased GER in this study is due to a larger catheter size (8F in preterm baby). In our cohort, 20 preterm infants were receiving NG feeds (size of NG tube 5F) whereas the other 20 were on full PO feeds during MII-pH study. We found no differences in number and characteristics of reflux episodes between the 2 groups. In addition to this, the acid exposure time was also similar in infants receiving NG feed versus PO feed. The common signs and symptoms attributed to reflux during infancy are not specific for GERD. Several investigators have attempted to correlate symptoms in infants with reflux episodes detected by MII-pH study with conflicting results (4,11–13). Moreover, these studies were small, with a shorter duration of monitoring, and correlated fewer signs and symptoms. In a study on 19 preterm infants, apnea, bradycardia, or desaturation had no temporal correlation with reflux episodes (12). Wenzl et al (11), using SI and SSI to correlate apnea with reflux episodes in 22 infants, found that apnea was correlated with reflux episodes in 13.7% by SI and 54.5% by SSI. In a similar study, only 15.2% of apnea episodes were correlated with GER, and SAP was positive only in 4 of 25 infants (15). On the contrary, Conidino et al (13) reported a higher correlation with any symptoms (SI, 66% of infants and SSI 53.3% of infants) in 34 infants referred for evaluation

of GER. Ours is the largest study investigating the temporal relations of a variety of common, nonspecific signs and symptoms with reflux episodes as detected by MII-pH study during 16 to 24 hours. A wide range of time intervals (20 seconds to 5 minutes) between symptoms and reflux episodes have been used for temporal relation (11–13,15,30). Similar to other investigators, we used a generous time interval (5 minutes before and 5 minutes after) to maximize the correlation between symptoms and reflux episodes (11,16). In addition, we used the presence of any refluxate into the esophagus to define a reflux episode compared with others who strictly use reflux episodes that reach the proximal esophagus for symptom association. Temporal association in our study was evaluated using all the 3 indices (SI, SSI, and SAP). Despite our most liberal approach, we did not find a temporal link between signs and symptoms commonly attributed to GER with reflux episodes. A temporal relation with reflux was established in only 1 in 20 (5%) infants with bradycardia and 6 of 32 (19%) infants with irritability. Gagging was the only symptom with positive correlation in more than 50% of infants. Arching and feeding, difficulty while commonly attributed to GERD, had poor temporal correlation with reflux events in our study.

The diagnostic accuracy of the MII-pH study may best be evaluated by the use of the SI and the SAP, which in our study appeared well correlated and the most predictive. The present study is in contrast to other studies in infants where no correlation between SI, SSI, and SAP were found (31). Although in adults there was no correlation of SI with symptoms, SAP and SSI were significantly related to symptomatic response; however, it was far from ideal with low positive predictive value (PPV) and negative predictive value (NPV) (32). Correlation of MII-pH and reflux related symptoms is better in younger infants compared with older children and adults (33).

Acid suppression therapy reduced the number of episodes of acid reflux, but had no impact on the total number of reflux events. Similarly, Turk et al (34) reported that, while proton pump inhibitors decreased the acidity of refluxate in children and adolescents, they did not affect the total number of reflux episodes. MII-pH study, in contrast to a pH probe, is useful in evaluating symptoms associated with reflux even in the presence of acid suppression (5). Our study did not show differences in symptom association in infants with and without acid suppression therapy. The number of infants receiving acid suppression therapy, however, was too small. A larger study is needed to evaluate the effects of acid suppression therapy on symptoms related to acidic reflux (arching, irritability, and difficulty in feeding).

The present study has limitations. This is a retrospective analysis from a single center of infants with a high index of suspicion for reflux. Based on the patient selection, we cannot provide reference values in the general infant population nor can we validate the symptom-reflux association analysis parameters. This review included preterm infants on oral, as well as NG feeding. Another important limitation is interobserver and intraobserver variability in interpretation of MII data. A validated automated computer analysis may improve reliability in interpretation of MII data. The strengths of our study include: the largest sample size of preterm and term infants, the number of clinical symptoms evaluated and correlated with reflux episodes, the duration of the MII-pH study, and use of the sensitive tool (SAP) for correlation.

In conclusion, the present study indicates that in preterm and term infants with strong clinical suspicion for reflux, the prevalence of significant GER as detected by MII-pH was low. The incidence and pattern of GER was similar in preterm and term infants. The presence of small-bore NG tube was not associated with increased GER in preterm infants. The majority of suspected clinical reflux behaviors did not correlate directly to actual reflux events. MII-pH study can be useful in these infants before initiating therapy for GERD. In infants with no temporal relation between symptoms and reflux episodes, other etiologies for reflux-like behavior should be sought.

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What Is Known

- Gastroesophageal reflux is common in preterm and term infants.
- Multichannel intraluminal impedance studies have become the criterion standard for the diagnosis of gastroesophageal reflux.
- A variety of signs and symptoms in preterm and term infants have been attributed to gastroesophageal reflux.

What Is New

- In preterm and term infants with strong clinical suspicion for reflux, the prevalence of significant gastroesophageal reflux as detected by multichannel intraluminal impedance studies is low.
- The incidence and pattern of gastroesophageal reflux is similar in preterm and term infants.
- Nasogastric tube does not increase gastroesophageal reflux episodes and acid exposure in preterm infants.
- The majority of suspected clinical reflux behaviors do not correlate with reflux events.

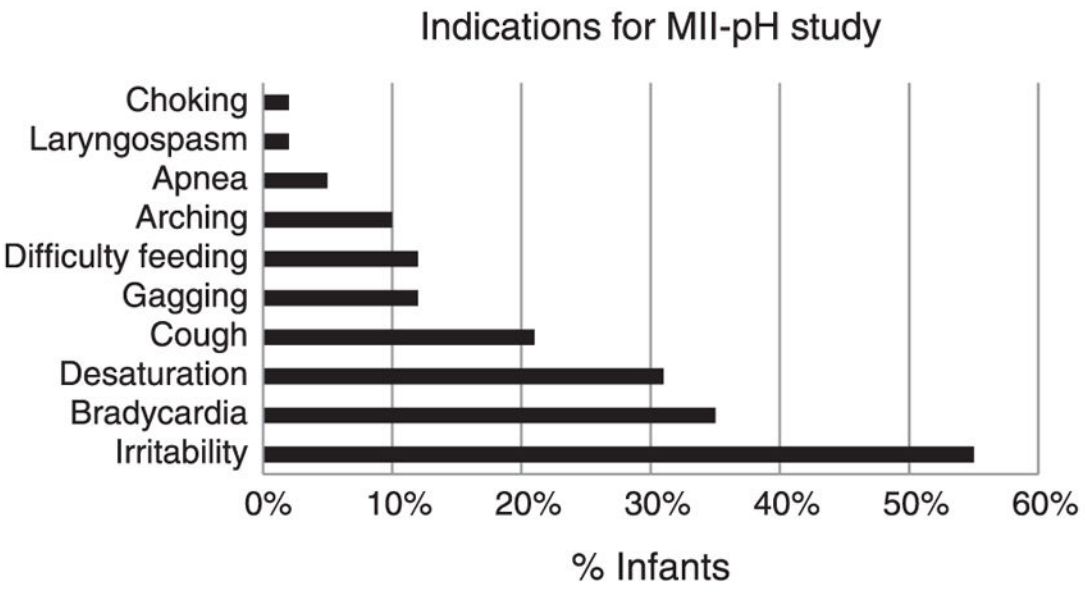

FIGURE 1.

Indications for MII-pH study in the study population expressed in percentage (some infants had more than 1 indication for MII-pH study). MII-pH = multichannel intraluminal impedance study.

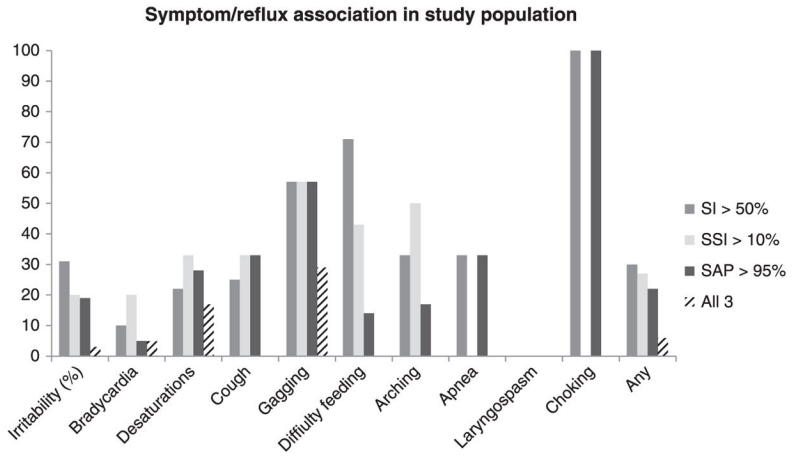

FIGURE 2.

Symptom/reflux association in the study population representing percent of infants with SI > 50%, SSI > 10%, SAP > 95% and all of the 3 for each sign or symptom. SI = percentage of symptoms related to GER episode; SSI = percentage of GER episodes associated with symptom; SAP = symptom association probability.

TABLE 1

Demographics and clinical characteristics (n = 58)

Gestational age, wk (median, range)	31 (23–40)
Birth Weight in grams (median, range)	1683 (430–4440)
Male sex (%)	28 (48)
White race (%)	25 (43)
Term (%)	18 (31)
Preterm (<37 wk) (%)	40 (69)
Age of study in days (median, range)	70 (1–330)
Duration of study, h (mean± SD)	18.3 ±3.7

TABLE 2

GER events recorded during MII-pH study (median, IQR) (n = 58)

	During study period	Per hour
Acid reflux	12 (6–21)	0.67 (0.34–1.18)
Weakly acid reflux	20 (9–34)	1.09 (0.54–1.61)
Total (acid + weekly acid)	37 (21–52)	2.03 (1.28–2.86)
% of time pH < 4 (median, range)	2.6 (0.5–5.5)	
Number of infant total episodes >55 or >3.0/h (%)	9 (15.5)	13 (22.4)
Number of infant total episodes >75 or >4.2/h (%)	6 (10.3)	4 (6.9)
Number of infants with acid exposure >5%	18 (31)	
Number of infants with acid exposure >20%	2 (3.5)	
Number of infants with total episodes >75 or >4.2/h acid exposure >20%	8 (13.7)	6 (10.3)

GER = gastroesophageal reflux; IQR = interquartile range; MII-pH = multichannel intraluminal impedance study.

TABLE 3

GER events recorded during MII-pH study in preterm and term infants

	Preterm (n = 40)	Term (n= 18)	*P*
Gestational age, wk	29 (23–36)	39 (37–40)	<0.001
Age of study, days	86 (4–228)	69 (1–330)	0.4
Acid reflux per hour (median, IQR)	0.59 (0.32–1.19)	0.79 (0.49–1.14)	0.97
Nonacid reflux per hour (median, IQR)	0.82 (0.42–1.51)	1.18 (0.92–2.06)	0.37
Total (acid + nonacid) per hour (median, IQR)	1.97 (1.18–2.63)	2.27 (1.61–3.17)	0.53
% of time pH < 4 (median, IQR)	3.0 (0.6–6.3)	1.4 (0.4–4.5)	0.4
Number of infant with episodes >3.0/h (%)	8 (20.0)	5 (27.7)	0.5
Number of infant with episodes >4.2/h (%)	3 (7.5)	1 (5.5)	1.0
Number of infants with acid exposure >5%	14 (35)	4 (22)	0.4
Number of infants with acid exposure >20%	1 (2)	1 (5)	0.5
Number of infants with episodes >4.2/h or acid exposure >20%	4 (10)	2 (11)	1.0

GER = gastroesophageal reflux; IQR = interquartile range; MII-pH = multichannel intraluminal impedance study.

TABLE 4

Relation between symptoms and reflux events reported as SI, SSI, and SAP

Symptoms	No. of infants (No. of events)	SI Med (IQR)	SSI Med (IQR)	SAP Med (IQR)
Irritability	32 (372)	30 (14–42)	7.3 (2.5–13.7)	82 (0–94)
Bradycardia	20 (122)	0 (0–26)	0.9 (0–2.8)	0 (0–29)
Desaturation	18 (94)	3 (0–69)	1.5 (0–6.3)	0 (0–97)
Cough	12 (158)	23 (0–43)	7.1 (2.6–16.0)	87 (46–95)
Gagging	7 (42)	47 (33–52)	10.3 (4.3–12.9)	94 (63–98)
Difficulty feeding	7 (52)	75 (43–97)	8.5 (3.9–21.7)	66 (27–74)
Arching	6 (85)	30 (22–45)	10.0 (5.2–11.1)	41 (9–75)
Apnea	3 (18)	7 (3–37)	1.9 (0.9–3.7)	38 (19–68)
Laryngospasm	1 (5)	8.9	40	0
Choking	1 (5)	7.0	60	100
All	(953)	28 (0–50)	3.7 (0–10.5)	62 (0–94)

SI = symptom index; SSI = symptom sensitive index; SAP = symptom association probability; IQR = interquartile range.