The Characteristics of Esophageal Multichannel Intraluminal Impedance-PH Measurements in Infants Experiencing Brief Resolved Unexplained Events

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Abstract

Background: Brief Resolved Unexplained Events (BRUE) is defined as a sudden, brief and now resolved episode characterized by color change, altered respirations, change in tone, and altered level of responsiveness. This study aims to identify the characteristics of esophageal Multichannel Intraluminal Impedance-pH (MII-pH) monitoring in infants who have experienced a BRUE.

Methods: This study was a retrospective review of records of infants younger than 12 months who presented to the University of South Alabama Children's and Women's Hospital with an admission diagnosis of BRUE. Patients who underwent esophageal MII-pH monitoring between October 2015 and February 2017 and diagnosed with BRUE were initially included in this study.

Results: Fifty-three infants (preterm 25, term 28) who experienced a higher risk BRUE were included in our study. The mean age at diagnosis was 2.25 ± 2.07 months. Apnea (41/53; 77.4%) was the most common manifestation of BRUE. Non-acid reflux events were the most common findings in the MII-pH studies (66%). MII-pH results showed 6/53 (11%) acid reflux, 17/53 (32%) non-acid reflux and 12/53 (23%) both acid/nonacid reflux and 18/53 (34%) were normal. There

were significant differences in the longest acid reflux episode and the Reflux Symptom Sensitivity Index (RSSI) of coughing/choking/gagging between preterm and term infants. The Reflux Symptom Index (RSI), RSSI and Reflux Symptom Association Probability (RSAP) were significantly correlated with each other in all symptoms (pain/fussiness, coughing/choking/gagging and vomiting).

Conclusions: Among infants experiencing a higher risk BRUE, esophageal MII-pH monitoring revealed acid or nonacid reflux in 2/3 of patients.

Keywords

Brief resolved unexplained events; Apparent life-threatening events; Multichannel intraluminal impedance-pH study; Gastroesophageal reflux disease; Infants

Introduction

Brief Resolved Unexplained Events (BRUE) is a replacement of the previous term Apparent Life-Threatening Events (ALTE). The term "BRUE" is defined as a sudden, brief and now resolved episode occurring in an infant younger than 1 year that is frightening to the parent/guardian and the episode is characterized by color change, altered respirations, change in tone, and altered level of responsiveness [1]. Infants who have experienced a BRUE are categorized based on history and physical examination as lower risk for whom evidenced-based guidelines support limited intervention and higher risk BRUE for whom further diagnostic testing is indicated. Gastroesophageal reflux disease (GERD) may be associated with higher risk BRUE, in cases when extra-esophageal symptoms of apnea, oxygen desaturation, and chronic airway symptoms occur [1].

The association between GERD and apnea of BRUE is still controversial. Diagnostic evaluation for GERD is not recommended for all infants with a higher risk BRUE. GERD and apnea are both common in premature infants. Since the esophageal Multichannel Intraluminal Impedance-pH (MII-pH) study can be helpful in correlating acid and non-acid reflux events with GERD symptoms in pediatric patients. It can offer better clarification than a pH study, which can only detect acid reflux.

The relationship of esophageal reflux to findings in MII-pH studies is not clear in connection with higher risk BRUE. Therefore, the objective of this present study was to correlate the characteristics of esophageal MII-pH monitoring in preterm and term infants who experienced a higher risk BRUE.

Materials and Methods

Study population

This study was a retrospective review of records of infants younger than 12 months who presented to the University of South Alabama Children's and Women's Hospital with an admission diagnosis of BRUE between from October 2015 to February 2017. The Institutional Review Board of the University of South Alabama approved the study.

Data collection

Infants were identified from a query of medical records using the ICD-10 code for ALTE or BRUE (R68.13). Initially, two investigators (C.J., M.G.) each reviewed the electronic medical records to ensure consistent data. Patients who underwent esophageal MII-pH monitoring between October 2015 and February 2017 and diagnosed with ALTE or BRUE were initially included in our study.

The demographics, gestational age, past medical history (including congenital heart disease, genetic diseases, bronchopulmonary dysplasia, and preexisting known GERD), BRUE details at initial presentation, feeding history, growth parameters, length of hospitalization and MII-pH study results were collected. We defined preterm infants were less than 37 weeks of gestational age.

Multichannel Intraluminal Impedance-pH (MII-pH) study data

Esophageal impedance-pH catheters with a 2.13 mm diameter containing 7 impedance sensors (ComforTEC, Sandhill Scientific, Inc. Highlands Ranch, CO) were used for the study. MII-pH data were collected utilizing a ZepHr recorder (Sandhill Scientific) and analyzed with BioView version 1.2 software (Sandhill Scientific). The tip of MII-pH catheter was confirmed by a chest x-ray between T7-T9. Parents/guardians were instructed on how to record symptoms since the study was performed in both the inpatient setting. Proton pump inhibitors were discontinued for 7 days and histamine 2-receptor antagonists were stopped at least 48 hours prior to esophageal MII-pH monitoring. After completion of the study, the data were reviewed and analyzed by the three pediatric gastroenterologists. Esophageal reflux events were defined by a retrograde fall in impedance > 50% from baseline for at least two distal channels. The reflux was classified as acid (pH<4), or non-acid based on simultaneous pH monitoring. A symptom-reflux association analysis from the data was performed to assess for a temporal association between parent-reported symptoms and esophageal reflux events. The parameters collected for analysis included the following:

- Acid Reflux episodes = a decrease in pH below 4 that lasts for more than 10 seconds.

- Non-acid Reflux episodes = retrograde fall in impedance > 50% from baseline for at least two distal channels with simultaneous pH measurement >4.

- Reflux Index (RI) = the percentage of time that the esophageal pH was < 4 during the study (total esophageal acid exposure). Normal value < 5.4%.

- Impedance Score (IS) = total number of acid and nonacid esophageal reflux events. Normal value is < 73.

- Euler Byrne score (EBS) = number of reflux episodes + (4 x number of episodes of 5 minutes). Normal value is < 50.

- Boix-Ochoa score = integration of the mean duration of the episodes of reflux, the clearance time and the total time of gastroesophageal reflux. Normal value is < 16.6.

- Longest acid episode = the duration of reflux episodes lasting longer than 5 minutes. Normal value is < 5 minutes.

- Reflux Symptom Index (RSI) = the percentage of symptoms related to esophageal reflux episodes or defined as (number of reflux related symptom episodes/total number of symptom episodes) x 100%. Normal value is < 50%.

- Reflux Symptom Sensitivity Index (RSSI) = the percentage of reflux episodes associated with symptoms or defined as (number of symptom associated reflux episodes/total number of reflux episodes) x 100%. Normal value is < 10%.

- Reflux Symptom Association Probability (RSAP) = the statistical means (Fisher exact test) of calculating the probability that the symptoms and reflux episodes are related. Normal value is < 95%.

We investigated the characteristics of MII-pH analysis and correlation between the number of acid reflux or non-acid reflux episodes, mean acid clearance time (seconds), Boix-Ochoa score, longest acid reflux episode (minutes), reflux index, impedance score, and Euler-Byrne score, as well as the RSI, RSSI, and RSAP for each of the following symptoms: pain/fussiness, coughing/choking/gagging and vomiting associations. We also compared the differences in characteristics of MII-pH parameters between preterm and term infants who experienced a higher risk BRUE.

Statistical analysis

For quantitative variables, data are shown as the mean ± standard deviation (SD) and a t-test was used to compare whether the two means were significantly different. If the normality assumption is violated, a WilcoxON test was used to test whether the two medians were significantly different. For the qualitative variables, we performed Fisher's exact test for testing the null hypothesis that the distributions in the two diseases are the same. Spearman's correlation coefficients were used to study the correlation between two quantitative variables.

Results

Demographic, clinical characteristics of infants

Medical record review showed that 53 of 132 (40%) infants presenting with higher risk BRUE underwent esophageal MII-pH study from October 2015 to February 2017. These infants ranged from 7 days to 12 months of age (mean 2.25 ± 2.07 months) and were included in this study. Most infants were female (28/53; 52.8%) and Caucasian (33/53; 62.3%) with a mean gestational age of 35.50 ± 3.5weeks.The mean birth weight was 2.4 ± 0.80 kilograms. The presenting symptoms included apnea (41/53; 77%), cyanosis (25/53; 47%), choking (16/53; 30%), back arching (9/53; 17%), gagging (2/53; 4%), and coughing (2/53; 4%). There were 28/53 (53%) term infants and 25/53 (47%) preterm infants. The mean weight, length and head circumference at the time of BRUE diagnosis were 4.2 kilograms, 52.6 centimeters and 37.2 centimeters, respectively. The most common diets were a cow milk-based formula (19/53; 36%) or an extensively hydrolyzed formula (12/53; 23%). The most common underlying disease was GERD (21; 40%). Moreover, GERD was

reported in 5 radiographic and fluoroscopic evaluations of upper GI tract contrast studies (4/5; 80%). Four infants underwent video fluoroscopic swallow studies that were normal. Histamine 2-receptor antagonists were prescribed for 38/52 (72%), which was the most common medication after discharge. In follow up, there were 3 infants who experienced recurrent BRUE episodes after discharge associated with GERD (2) and apnea of prematurity (1). No complication after the MII-pH procedure (Table 1).

Analysis of MII-pH data

Examination of the MII-pH data detected a total of 3,436 gastroesophageal reflux episodes of which 1,181 were acid (34%) and 2,255 were non-acid (66%). There were 247/602 (41%) pain/fussiness episodes that were related to reflux; 240/482 (50%) coughing/choking/gagging episodes that were related to reflux; and 106/199 (53%) vomiting episodes that were related to reflux. Table 2 showed the characteristics of the gastroesophageal reflux symptom episodes and parameters of the MII-pH studies. Only the mean longest acid episode (11.5 minutes) was above the normal value (5 minutes). Other parameter means were within normal limits. The final result of MII-pH studies showed that esophageal reflux within the physiologic range was detected in 18/53 (34%) infants, while 6/53 (11%) were positive for acid reflux, 17/53 (32%) were positive for non-acid reflux and 12/53 (23%) were positive for both acid and nonacid reflux. Analysis of the association between pain/fussiness, coughing/choking/gagging, and vomiting with esophageal reflux were depicted in Table 2. In addition, a clinical diagnosis of GERD was suspected prior to admission in 17/35 (49%) of patients who had a positive result from their MII-pH study, indicating that higher risk BRUE was the initial presenting symptom in approximately half of infants who were diagnosed with GERD based on esophageal MII-pH monitoring.

Comparison of MII-pH data between preterm and term infants

As expected, there were significant differences in the mean values of the gestational age, birth weight, length, and head circumference at the time of diagnosis of higher risks BRUE between preterm and term infants. There were no significant differences in the number of acid, non-acid and all reflux episodes between preterm and term infants. Interestingly, preterm infants showed more delayed esophageal acid clearance with a mean longest acid reflux episode of 14.6 ± 12.3 minutes compared to that of term infants (8.7 ± 12.9 minutes; p value 0.02). In addition, the RSSI for coughing/choking/gagging events during acid, non-acid and all esophageal reflux episodes in preterm infants was significantly higher than in term infants (Table 3). The comparison of other characteristics and MII-pH parameters between preterm and term infants were depicted in Table 3.

Correlation of symptom-reflux association analysis

There were significant correlations between the number of acid reflux episodes and all MII-pH parameters including the mean acid clearance time, Boix-Ochoa score, longest acid reflux episode, EBS, along with the RSI, RSSI and RSAP of acid reflux-related pain/fussiness, coughing/choking/gagging, and vomiting. In contrast, non-acid reflux episodes and all esophageal reflux episodes were only significantly correlated with the RSI pain/fussiness and coughing/choking/gagging, while the RSSI was only significantly associated with reflux related pain/fussiness and coughing/choking/gagging. Only the RSI, RSSI, and

RSAP for reflux-vomiting symptoms were not correlated with non-acid or all esophageal reflux episodes. RSAP was the parameter least likely to show significant correlations among the indices analyzed for symptom association (RSI, RSSI, RSAP). Moreover, this present study showed that the RSI and RSSI for pain/fussiness and coughing/choking/gaggingsignificantly correlated with the number of acid, nonacid and all esophageal reflux episodes (Table 4).

The mean acid clearance time was the second most common parameter that significantly correlated with other parameters of the MII-pH study including the number of acid reflux episodes, number of all esophageal reflux episodes, the Boix-Ochoa score, the longest acid episode, the RI and EBS, along with the RSI and RSSI for coughing/choking/gagging and the RSSI for pain/fussiness and vomiting. Moreover, the RI correlated with the mean acid clearance time, the Boix-Ochoa score, the longest acid reflux episode, IS and EBS. Interestingly, the RI did not correlate with any symptom correlation analysis (RSI, RSSI, RSAP). Conversely, IS was significantly correlated with the RSI and RSSI for pain/fussiness and coughing/choking/gagging with non-acid episodes and all esophageal reflux episodes.

Correlation among symptoms of pain/fussiness, coughing/choking/gagging and vomiting with the RSI, RSSI, and RSAP

There were significant correlations during the pain/fussiness, cough/gag/choke and vomiting eventsand the RSI, RSSI, and RSAP association parameters. Only the RSAP for pain/ fussiness and vomiting were not correlated significantly. Interestingly, the RSI, RSSI and RSAP were significantly correlated with each other in all symptoms (pain/fussiness, cough/gag/choke and vomiting). However, the correlation was strongest between RSI and RSAP in all symptoms (Table 5).

Discussion

Multiple studies have reported an association between GERD and ALTE. One large study that analyzed 12,067 ALTE admissions showed that 36.9% of infants were given a primary diagnosis of GERD at discharge. However, in that study, only 8.9% of patients underwent esophageal pH monitoring, while 25.6% were reported to have esophageal reflux based on an upper gastrointestinal study or swallow study [2]. A study by Zimbric et al. [3] reported that a GERD diagnosis and positive reflux test during hospitalization in infants with ALTE were not related to complications of GERD such as aspiration pneumonia, failure to thrive or the need for anti-reflux surgery.

Blasco-Alonso J et al. [4] reported that 33/39 (85%) of infants with ALTE who underwent esophageal MII-pH monitoring were diagnosed with GERD, which is in contrast to the present study (66%).That report also revealed the number of non-acid reflux episodes was more dominant than acid reflux episodes, which was similar to this present study. Furthermore, other studies have shown that nonacid reflux was more common than acid reflux events in preterm and term infants who experienced apnea or ALTE [5–8]. This observation confirms the value of esophageal MII-pH monitoring when correlating symptoms with esophageal reflux events in infants with apnea or BRUE.

The reason for a relationship between GERD and apnea is not clear. One hypothesis is that esophageal reflux may lead to apnea due to fluid or acid stimulation of the laryngeal mucosa which can trigger laryngospasm to prevent aspiration. In addition, cardiorespiratory reflexes from receptors in the esophageal mucosa in response to reflux of gastric contents. Furthermore, aspiration induced bronchospasm is often associated with apnea. An alternate theory is that apnea may trigger reflux because hypoxia may decrease the lower esophageal sphincter tone that predisposes to reflux of gastric contents into the esophagus [9].

A casual relationship between GERD and BRUE has not been established. There are many studies that show no causal association between ALTE or apnea and GERD, in either preterm or term infants [6,10–16]. Despite the lack of a cause and effect relationship, infants frequently undergo diagnostic evaluation for GERD and are widely prescribed anti-reflux medications. One systematic review showed that routine testing for GERD is unnecessary in infants who are well appearing. Infants with recurrent ALTE may benefit from esophageal MII-pH monitoring combined with polysomnography to evaluate for a temporal relationship between esophageal reflux and respiratory symptoms or assessment for other causes [17].

Sankaran J et al. [18] reported on 25 infants presenting with BRUE who underwent concurrent MII-pH and video-polysomnography. That study showed that increases in RI were significantly associated with acid clearance time and the RSI for respiratory symptoms during wake or sleep states. The RI in this present study correlated with the mean acid clearance time but there was no significant association with any symptom-based analyses such as RSI, RSSI, or RSAP.

One limitation of RSI and RSSI is that they are affected by the frequency of events. The RSI is likely to be positive when the number of reflux episodes is increasingly high and the RSSI is prone to be positive when the number of symptom events is elevated [19]. RSAP is a better parameter due to calculating relationships between symptoms and reflux [19]. In this present study, RSI, RSSI and RSAP significantly correlated with each other in all symptoms (pain/fussiness, coughing/choking/gagging, and vomiting) and that RSI and RSAP had the strongest correlation as was similar to a study by Funderburk et al. [20]. The current study found only that the longest acid reflux episode and the RSSI of coughing/choking/gagging was significantly higher in preterm infants than term infants. These differences between the present study and the Funderburk report [20] between preterm and term infants may be due to the fact that the current study investigated infants presenting with BRUE instead of infants suspected to have GERD.

Hasenstab et al. [21] reported that prolonged spontaneous respiratory events are associated with ineffective esophageal motility in infants with ALTE. They measured motility by pharyngo-esophageal manometry in 10 infants with ALTE compared to 10 healthy controls. Thus they suggested that infants with ALTE most likely have dysfunctional regulation of swallow-respiratory coordination and that treatment should not only focus on GERD, but also the proximal aero-digestive tract. However, the association between aero-digestive mechanisms and BRUE remains unclear. Furthermore, Duncan et al. [22] reported a study of 188 infants with ALTE of which 55 (29%) underwent video fluoroscopic swallow studies where 40/55 (73%) showed evidence of aspiration or penetration, leading to the conclusion

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that oropharyngeal dysphagia with aspiration is one of the diagnoses of infants presenting with ALTE and symptoms of oropharyngeal dysphagia which mimic symptoms of GERD [22]. The current study found normal results in a small subset of subjects who underwent video fluoroscopic swallow studies (4/53; 7.5%).

GERD and milk soy protein intolerance (MSPI) are frequent disorders in infants. A possible association between GER and MSPI has been suggested. Up to 40% of infants with GER are noted to have MSPI [23]. We speculate that MSPI also may be associated with BRUE because infants with MSPI can have symptoms of vomiting and retching that disrupt the normal gastric motor activity and can lead to apnea or cyanosis.

There were several limitations of this study. First, this was a retrospective study, which could be subject to bias and incomplete/missing data. Second, our study had a small subject pool of only 53 infants with BRUE who underwent esophageal MI-pH monitoring. Third, this study was carried out at a single teaching hospital, which may limit the applicability of these results to other settings. Fourth, we did not combine polysomnography during the MII-pH study that might determine etiologies other than GERD causing a BRUE. Fifth, unfortunately, normal values for esophageal MII-pH monitoring for infants have not yet been established so we used these normal parameter values from adult studies.

In conclusion, this is the first study to assess characteristics and to correlate parameters of esophageal MII-pH monitoring in preterm and term infants with BRUE. Among infants experiencing a BRUE, MII-pH monitoring revealed acid or nonacid reflux in 2/3 of patients. This study showed nearly similar characteristics of esophageal MII-pH monitoring in preterm and term infants presenting with higher risk BRUE. Acid and non-acid reflux episodes in infants may be physiologic and may resolve without treatment. The diagnosis of GERD in these infants may lead not only to unnecessary treatment, but may delay detection of other serious disorders. GERD and BRUE may simply occur coincidentally. Future studies are indicated to investigate the potential role of esophageal MII-pH monitoring in infants who experienced higher risk BRUE with suspected GERD.

Acknowledgement:

Abbreviations:

BRUE	Brief Resolved Unexplained Events
ALTE	Apparent Life-Threatening Events
MII-pH	Multichannel Intraluminal Impedance-Ph
GERD	Gastroesophageal Reflux Disease
RI	Reflux Index
IS	Impedance Score

EBS	Euler-Byrne Score
RSI	Reflux Symptom Index
RSSI	Reflux Symptom Sensitivity Index
RSAP	Reflux Symptom Association Probability

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Summary Box

What is Known on this subject

- Gastroesophageal reflux disease (GERD) is one of the conditions associated withhigher risk Brief Resolved Unexplained Events (BRUE).

- Multichannel Intraluminal Impedance-pH (MII-pH) can be helpful in correlating symptoms with esophageal reflux events

- Diagnostic testing for GERD is not recommended for all infants with BRUE.

What are the new findings

- Among infants experiencing a higher risk BRUE, MII-pH monitoring revealed acid or nonacid reflux in 2/3 of patients.

- There was a significant correlation between the number of acid reflux episodes and all MII-pH parameters in infants presenting with BRUE.

- There were significant correlations between symptoms of pain/fussiness, coughing/choking/gagging, and vomiting with symptom association analyses including the Reflux Symptom Index (RSI) and the Reflux Symptom Sensitivity Index (RSSI) but not the Reflux Symptom Association Probability (RSAP).

- The Reflux Symptom Index (RSI), Reflux Symptom Sensitivity Index (RSSI) and Reflux Symptom Association Probability (RSAP)were significantly correlated with each other in all symptoms (pain/fussiness, coughing/choking/ gagging. and vomiting) and the correlation was strongest between RSI and RSAP in all symptoms.

Table 1:

Demographic, clinical characteristics of infants who experienced BRUE.

Characteristics	Result (N=53)
1. Gender (%)	
- Male	25 (47.2%)
- Female	28 (52.8%)
2. Ethnicity (%)	
- Caucasian	33 (62.3%)
- African American	19 (35.8%)
- Hispanic	1 (1.9%)
3. Age at diagnosis of BRUE in months (mean ±SD)	2.3 ± 2.1
4. Gestation age in weeks (mean ±SD)	35.5 ± 3.5
	28 (52.8%)
5. Term infants (%)	25 (47.2%)
Preterm infants (%)	2.44 ± 0.80
6. Birth weight in kilograms (mean ±SD)	6 (11.3%)
	47 (88.7%)
7. Small for gestational age (%)	
Appropriate for gestational age (%)	41/53 (77.4%)
8. Presentation of BRUE (%)	25/53 (47.2%)
- Apnea	16/53 (30.2%)
- Cyanosis	9/53 (17%)
- Choking	2/53 (3.8%)
- Back arching	2/53 (3.8%)
- Cough	4.2 ± 1.7
- Gagging	
9. - Weight at diagnosis of BRUE in kilograms (mean ± SD)	52.6 ± 9.9
- Length at diagnosis of BRUE in centimeters (mean ± SD)	37.2 ± 3.7
- Head circumference of BRUE in centimeters (mean ± SD)	21 (39.6%)
10. Underlying diseases (%)	9 (17%)
- GERD	5 (9.4%)
- Milk soy protein intolerance	2 (3.7%)
- ASD	2 (3.7)
- VSD	4 (7.5%)
- Apnea of prematurity	
- Others [*]	19 (36%)
11. Formula (%)	12 (23%)
- Cow milk-based formula	11 (21%)
- Extensively hydrolyzed formula	9 (17%)
- Breast milk	2 (4%)
- 100% amino acid-based formula	5.10 ± 5.36
- Others [**]	
12. Length of stay in days (mean ± SD)	1 (20%)

Characteristics	Result (N=53)
13. Radiographic and fluoroscopic evaluation of upper GI tract (%)	4 (80%)
- Normal	4 (100%)
- GERD	
14. Video fluoroscopic swallow study	22 (42%) 8 (15%)
- Normal	23 (43)
15. Stool occult blood test (%)	
- Negative	38/53 (72%)
- Positive	6/53 (11%)
- Not done	
16. Medication after discharge (%)	
- Histamine 2 receptor antagonist	
- Proton-pump inhibitor	

[*] Criduchat (1), seizure disorder (1), sickle cell disease (1), and bronchopulmonary dysplasia (1)

[**] Soy formula (1), and regular diet (1)

BRUE: Brief Resolved Unexplained Events; GERD: Gastroesophageal Reflux Disease.

Table 2:

Multichannel Intraluminal Impedance-pH (MII-pH) study data in BRUE infants.

The MII-pH analysis data	Results (Mean ± SD)
1. Analysis duration (hours)	22.78 ± 1.18
2. Number of acid reflux episodes	22.28 ± 18.33
3. Number of non-acid reflux episodes	42.54 ± 26.69
4. Number of all reflux episodes	64.77 ± 25.56
5. Number of all reflux distal episodes	67.10 ± 27.88
6. Number of all reflux proximal episodes	44.88 ± 20.95
7. Mean acid clearance time (seconds)	112.63 ± 119.17
8. Boix-Ochoa score	10.54 ± 9.79
9. Longest acid episode (minutes)	11.5 ± 12.81
10. RSI, all reflux (acid/non-acid)	
- Pain/fussiness	32.04 (9.47/24.66)
- Cough/gag/choke	38.91 (13.24/27.37)
- Vomiting	38.69 (9.50/30.94)
11. RSSI, all reflux (acid/non-acid)	
- Pain/fussiness	4.75 (3.68/5.07)
- Cough/gag/choke	5.05 (3.64/5.17)
- Vomiting	3.45 (2.07/3.70)
12. RSAP, all reflux (acid/non-acid)	
- Pain/fussiness	32.85 (17.04/25.81)
- Cough/gag/choke	58.38 (32.47/45.90)
- Vomiting	49.17 (21.73/42.92)
13. Reflux index	4.30 ± 4.17
14. Impedance score	71.66 ± 31.20
15. Euler-Byrne score	33.08 ± 28.28
16. Result of MII-pH (%)	
- Negative	18/53 (33.96%)
- Acid reflux	6/53 (11.32%)
- Non-acid reflux	17/53 (32.08%)
- Both acid and non-acid reflux	12/53 (22.64%)

RSI: Reflux Symptom Index; RSSI: Reflux Symptom Sensitivity Index; RSAP: Reflux Symptom Association Probability.

Table 3:

Characteristics and MII-pH indices in preterm and term infants in BRUE (mean ± SD).

	Preterm (n=25)	Term (n=28)	P value
Age at diagnosis of BRUE in months	1.84 ± 1.22	2.61 ± 2.57	0.41
Gestation age in weeks	33.3 ± 3.12	38.27 ± 0.94	**< 0.0001**
Birth weight in kilograms	1.98 ± 0.63	3.13 ± 0.50	**< 0.0001**
Weight at diagnosis of BRUE in kilograms	3.29 ± 1.05	5.07 ± 1.78	**< 0.0001**
Length at diagnosis of BRUE in centimeters	48.08 ± 9.87	56.70 ± 8.02	**< 0.0001**
Head circumference of BRUE in centimeters	35.53 ± 2.95	38.79 ± 3.75	**0.003**
Length of stay in days	6.00 ± 6.95	4.29 ± 3.31	0.408
Number of acid reflux episodes	21.84 ± 15.51	22.68 ± 20.82	0.721
Number of non-acid reflux episodes	49.08 ± 26.94	36.71 ± 25.55	0.065
Number of all reflux episodes	70.80 ± 27.96	59.15 ± 22.75	0.133
Mean acid clearance time	128.84 ± 118.75	98.16 ± 119.81	0.175
Boix-Ochoa score	11.72 ± 9.49	9.49 ± 10.11	0.262
Longest acid episode	14.63 ± 12.26	8.71 ± 12.85	**0.020**
RSI pain /fussiness acid reflux	6.92 ± 12.24	11.75 ± 18.05	0.352
RSI pain/fussiness nonacid reflux	25.68 ± 31.24	23.75 ± 33.68	0.564
RSI pain/fussiness all reflux	30.88 ± 31.59	33.07 ± 33.90	0.993
RSI cough/gag/choke acid reflux	12.72 ± 19.06	13.71 ± 30.29	0.739
RSI cough/gag/choke nonacid reflux	28.92 ± 29.40	26.00 ± 29.30	0.598
RSI cough/gag/choke all reflux	39.96 ± 31.74	38.11 ± 39.54	0.657
RSI vomiting acid reflux	9.96 ± 15.73	9.11 ± 16.68	0.464
RSI vomiting nonacid reflux	27.24 ± 31.53	34.25 ± 35.61	0.481
RSI vomiting all reflux	35.96 ± 38.54	41.14 ± 35.00	0.569
RSSI pain /fussiness acid reflux	6.40 ± 18.26	1.25 ± 5.50	0.296
RSSI pain /fussiness nonacid reflux	9.28 ± 21.77	1.32 ± 5.32	0.008
RSSI pain /fussiness all reflux	8.64 ± 20.30	1.29 ± 4.93	0.016
RSSI cough/gag/choke acid reflux	6.08 ± 12.29	1.46 ± 7.01	0.024
RSSI cough/gag/choke nonacid reflux	8.56 ± 20.66	2.14 ± 6.35	0.005
RSSI cough/gag/choke all reflux	8.00 ± 20.07	2.43 ± 7.72	0.004
RSSI vomiting acid reflux	3.96 ± 12.36	0.39 ± 1.17	0.038
RSSI vomiting nonacid reflux	6.24 ± 18.99	1.43 ± 3.89	0.084
RSSI vomiting all reflux	6.08 ± 19.28	1.11 ± 2.73	0.091
RSAP pain /fussiness acid reflux	14.08 ± 33.03	19.68 ± 36.09	0.451
RSAP pain /fussiness nonacid reflux	27.12 ± 44.45	24.64 ± 38.55	0.991
RSAP pain /fussiness all reflux	33.88 ± 46.32	31.93 ± 40.77	0.960
RSAP cough/gag/choke acid reflux	32.80 ± 44.89	32.18 ± 44.30	0.774
RSAP cough/gag/choke nonacid reflux	51.04 ± 44.26	41.32 ± 44.75	0.512
RSAP cough/gag/choke all reflux	60.48 ± 43.80	56.50 ± 46.96	0.905

	Preterm (n=25)	Term (n=28)	P value
RSAP vomiting acid reflux	30.96 ± 42.65	13.50 ± 33.71	0.122
RSAP vomiting nonacid reflux	39.20 ± 46.10	46.25 ± 47.59	0.562
RSAP vomiting all reflux	47.00 ± 47.77	51.11 ± 45.79	1.000
Reflux index	4.55 ± 3.88	4.09 ± 4.48	0.504
Impedance score	80.36 ± 32.62	63.89 ± 28.22	0.105
Euler Byrne score	37.98 ± 29.93	28.71 ± 26.50	0.219

RSI, Reflux Symptom Index; RSSI, Reflux Symptom Sensitivity Index; RSAP, Reflux Symptom Association Probability.

Table 4:

Correlation between MII-pH parameters in BRUE (P value).

	Number of acid reflux episode	Number of non-acid reflux episodes	Number of all reflux episodes	Mean acid clearance time (Second)	Boix-Ochoa score	Longest acid episode (Minute)	RI (%)	IS	EBS
Mean acid clearance time	0.43 (0.0013)	0.15 (0.2911)	0.28 (0.0454)	N/A	0.71 (<0.0001)	0.79 (<0.0001)	0.49 (0.0002)	0.25 (0.0682)	0.42 (0.0014)
Boix-Ochoa score	0.79 (<0.0001)	−0.21 (0.1340)	0.22 (0.1193)	0.71 (<0.0001)	N/A	0.81 (<0.0001)	0.76 (<0.0001)	0.20 (0.1482)	0.84 (<0.0001)
RSI pain / fussiness	0.51 (0.001)	0.63 (<0.0001)	0.45 (0.0008)	0.15 (0.2865)	0.05 (0.7078)	−0.005 (0.9677)	0.01 (0.9293)	0.43 (0.0011)	−0.03 (0.7951)
RSI cough/gag/choke	0.53 (<0.0001)	0.39 (0.0032)	0.35 (0.0099)	0.28 (0.0427)	0.23 (0.1033)	0.09 (0.5146)	0.05 (0.6878)	**0.30 (0.0262)**	0.15 (0.2851)
RSI vomiting	0.47 (0.0004)	0.25 (0.0753)	0.13 (0.3728)	0.09 (0.4988)	0.10 (0.4691)	−0.03 (0.8234)	−0.02 (0.8785)	0.0794 (0.5718)	0.02 (0.8952)
RSSI pain / fussiness	0.32 (0.0188)	0.42 (0.0017)	0.36 (0.0082)	0.36 (0.0074)	0.18 (0.1896)	0.27 (0.0552)	0.07 (0.6107)	**0.33 (0.0167)**	−0.02 (0.9103)
RSSI cough/gag/choke	0.42 (0.0018)	0.32 (0.0280)	0.45 (0.0007)	0.43 (0.0013)	0.38 (0.0044)	0.37 (0.0066)	0.23 (0.0957)	**0.40 (0.0028)**	0.19 (0.1622)
RSSI vomiting	0.32 (0.0193)	0.24 (0.0827)	0.21 (0.1258)	0.4179 (0.0018)	0.27 (0.0535)	0.2697 (0.0508)	0.08 (0.5604)	0.12 (0.3833)	0.05 (0.6995)
RSAP pain /fussiness	0.27 (0.0456)	0.41 (0.0021)	0.21 (0.1367)	0.23 (0.0943)	0.17 (0.2138)	0.13 (0.3473)	0.10 (0.4394)	0.19 (0.1524)	0.1106 (0.4304)
RSAP cough/gag/choke	0.50 (0.0001)	0.27 (0.0501)	0.1015 (0.4739)	0.15 (0.2787)	0.12 (0.3976)	−0.01 (0.9297)	−0.03 (0.8381)	0.04 (0.7785)	0.09 (0.5033)
RSAP vomiting	0.33 (0.0148)	0.23 (0.0897)	0.10 (0.4653)	0.11 (0.4219)	0.05 (0.6775)	−0.08 (0.5761)	−0.07 (0.5967)	0.04 (0.7723)	−0.01 (0.9481)
RI (%)	N/A	N/A	N/A	0.49 (0.0002)	0.76 (<0.0001)	0.73 (<0.0001)	N/A	**0.28 (0.0413)**	0.76 (**<0.0001**)
IS	N/A	N/A	N/A	0.25 (0.0682)	0.20 (0.1482)	0.17 (0.2239)	0.28 (0.0413)	N/A	0.19 (0.1622)
EBS	0.75 (<0.0001)	−0.36 (0.0077)	0.09 (0.5315)	0.42 (0.0014)	0.84 (<0.0001)	0.64 (<0.0001)	0.76 (<0.0001)	0.19 (0.1622)	N/A

RI: Reflux Index; IS: Impedance Score; EBS: Euler Byrne score; RSI: Reflux Symptom Index; RSSI: Reflux Symptom Sensitivity Index; RSAP: Reflux Symptom Association Probability.

Table 5:

Correlation between pain/fussiness, cough/gag/choke, and vomiting symptoms and correlation between RSI, RSSI, and RSAP in BRUE (P value).

1. RSI	Pain/fussiness	Cough/gag/choke	Vomiting
Pain/fussiness	N/A	0.39 (P=0.004)	0.42 (P=0.002)
Cough/gag/choke	0.39 (P=0.004)	N/A	0.38 (P=0.005)
Vomiting	0.42 (P=0.001)	0.38 (P=0.005)	N/A
2. RSSI	**Pain/fussiness**	**Cough/gag/choke**	**Vomiting**
Pain/fussiness	N/A	0.5 (P=0.0004)	0.57 (P<0.0001)
Cough/gag/choke	0.5 (P=0.0004)	N/A	0.61 (P<0.0001)
Vomiting	0.57 (P<0.0001)	0.61 (P<0.0001)	N/A
3. RSAP	**Pain/fussiness**	**Cough/gag/choke**	**Vomiting**
Pain/fussiness	N/A	0.32 (P=0.02)	0.13 (P=0.36)
Cough/gag/choke	0.32 (P=0.02)	N/A	0.29 (P=0.035)
Vomiting	0.13 (P=0.36)	0.29 (P=0.035)	N/A
4. Pain/Fussiness	**RSI**	**RSSI**	**RSAP**
RSI	N/A	0.47 (P=0.0004)	0.67 (P<0.0001)
RSSI	0.47 (P=0.0004)	N/A	0.42 (P=0.0018)
⚡RSAP	0.67 (P<0.0001)	0.42 (P=0.0018)	N/A
5. Cough/gag/choke	**RSI**	**RSSI**	**RSAP**
RSI	N/A	0.57 (P<0.0001)	0.79 (P<0.0001)
RSSI	0.57 (P<0.0001)	N/A	0.44 (P=0.001)
RSAP	0.79 (P<0.0001)	0.44 (P=0.001)	N/A
6. Vomiting	**RSI**	**RSSI**	**RSAP**
RSI	N/A	0.49 (P=0.0004)	0.86 (P<0.0001)
RSSI	0.49 (P=0.0004)	N/A	0.51 (P=0.0004)
RSAP	0.86 (P<0.0001)	0.51 (P=0.0004)	N/A

RSI: Reflux Symptom Index; RSSI: Reflux Symptom Sensitivity Index; RSAP: Reflux Symptom Association Probability.