Original Article

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Esophageal Bolus Transit in Newborns with Gastroesophageal Reflux Disease Symptoms: A Multichannel Intraluminal Impedance Study

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Purpose: The aim of this study was to evaluate bolus transit during esophageal swallow (ES) and gastroesophageal reflux (GER) events and to investigate the relationship between the characteristics of ES and GER events in a population of term and preterm newborns with symptoms of gastroesophageal reflux disease (GERD).

Methods: The study population consisted of term and preterm newborns referred to combined multichannel intraluminal impedance (MII) and pH monitoring for GERD symptoms. The frequency and characteristics of ES and GER events were assessed by two independent investigators. Statistical significance was set at $p < 0.05$.

Results: Fifty-four newborns (23 preterm) were included in the analyses. Median bolus head advancing time corrected for esophageal length (BHATc) was shorter during mealtime than during the postprandial period (median, interquartile range): 0.20 (0.15-0.29) s/cm vs. 0.47 (0.39-0.64) s/cm, $p < 0.001$. Median bolus presence time (BPT) was prolonged during mealtime: 4.71(3.49-6.27) s vs. 2.66 (1.82-3.73) s, $p < 0.001$. Higher BHATc (p=0.03) and prolonged BPT ($p < 0.001$) were observed in preterm newborns during the postprandial period. A significant positive correlation between BHATc and bolus clearance time was also observed (ρ =0.33, p=0.016).

Conclusion: The analysis of ES and GER events at the same time by MII provides useful information to better understand the physiopathology of GERD. In particular, the analysis of BHATc during the postprandial period could help clinicians identify newborns with prolonged esophageal clearance time due to impaired esophageal motility, which could allow for more accurate recommendations regarding further tests and treatment.

Key Words: Esophageal swallow, Gastroesophageal reflux, Esophageal impedance, Newborn, Premature birth

INTRODUCTION

Gastroesophageal reflux (GER), defined as the involuntary passage of gastric contents into the esophagus, is a frequent physiologic event in healthy newborns and infants; when symptoms or lesions occur as a result of this reflux, it is referred to as gastroesophageal reflux disease (GERD) [1]. Impaired esophageal motility is one of the factors that contribute to the pathophysiology of GERD. In this context, transient lower esophageal sphincter relaxations are considered the main mechanism responsible for GERD, especially in preterm newborns [2]. However, prolonged esophageal clearance due to impaired esophageal motility contributes to the pathogenesis of GERD by causing prolonged esophageal exposure to refluxed material from the stomach and by contributing to the development of esophagitis and related symptoms [3].

Multichannel intraluminal impedance (MII) is a new technique for evaluating esophageal bolus transit in both adults and children [4]. MII allows for the detection of reflux events irrespective of their pH values, and allows for the determination of refluxate composition (liquid, gas, mixed), reflux duration and proximal extent [5]. Combined MII and pH monitoring (MII/pH) allows us to detect non-acid or weakly acidic reflux events, which are prevalent in newborns [6]. It has been shown that this technique can detect a higher number of reflux events than traditional pH-metry [7,8]. MII/pH is particularly suitable in newborns [9], and its application in term and preterm newborns with GERD symptoms has been shown to be safe and well tolerated [10]. While the role of MII in the study of GER is widely accepted, recently the possibility of using this technique to evaluate bolus transit during esophageal swallow (ES) has also been emerging [11,12].

The aim of this study was to evaluate bolus transit during ES and GER events in a population of term and preterm newborns with GERD symptoms using MII and to investigate the relationship between the characteristics of ES and GER events.

MATERIALS AND METHODS

In our study, we retrospectively considered a population of newborns consecutively admitted to our Neonatal Intensive Care Unit who underwent one 24-hour session of MII/pH for suspected GERD between December 2009 and March 2013. To be included in the study newborns had to meet the following inclusion criteria: Patients with clinical symptoms of GERD, as per criteria laid out in the North American Society for Pediatric Gastroenterology and Nutrition (recurrent vomiting and weight loss or poor weight gain, irritability, dysphagia or feeding refusal, apnea or ALTE, wheezing or stridor, cough, abnormal neck posturing) [13]; fed with breast milk or formula (thickened formulas were excluded); absence of congenital abnormalities, perinatal asphyxiation or neurological pathologies; no pharmacological therapy for GERD for at least one week; not taking any drug known to influence esophageal motor function.

MII/pH data (tracings) were recorded with a single-use esophageal probe with a pH-sensitive antimony electrode and seven integrated impedance electrodes, representing six impedance channels. The distance between each of the impedance electrodes was 1.5 cm and the pH sensor was situated in the distal impedance channel (channel 1), between the first and second impedance electrodes. Probes were calibrated and tested before each MII/pH session. The probe was placed in the esophagus transnasally, with the pH sensor located about 1.5 cm above the lower esophageal sphincter. A chest scan was performed to check the probe position, which was corrected when necessary. The number of MII channels present in the esophageal lumen was calculated, considering body length, according to Gupta and Jadcherla [14]. The impedance channels above the upper esophageal sphincter were excluded from the analysis and the first channel below the upper esophageal sphincter was defined as the proximal channel. During MII/pH infants were bottle fed with breast milk or formula approximately every 3 hours (daily average quantity of 150-160 mL/kg) and were

kept supine in their cots.

For the purposes of this study, only MII tracings were considered. The MII tracings from the beginning of the second feeding (mealtime) to 3 hours after the end of the meal (postprandial period) were visually analyzed by two independent investigators using Bioview Analysis software (Sandhill Scientific Inc., Highlands Ranch, CO, USA) to identify the frequency and characteristics of ES and GER events.

ES events

An ES event was identified as a rapid increase in impedance preceded by a drop in impedance to 50% of baseline beginning in the proximal channel and preceding in an anterograde direction to the most distal channel, followed by the recovery of baseline values at each channel [15]. The ES events detected by MII were grouped into mealtime events (the first nine consecutive ES events with no artifacts detected during mealtime) and postprandial period events (all ES events detected during the postprandial period).

The frequency of ES events (ES events/h) was measured, along with the following ES event characteristics:

• Bolus head advancing time (BHAT): time between the bolus entrance recorded in the proximal channel and the bolus entrance recorded in the distal channel, measured in seconds.

• BHAT corrected for esophageal length (BHATc): BHATc was calculated using the formula

$$BHATc = BHAT/esophageal\ length$$

expressed in s/cm, where esophageal length is the distance between proximal and distal impedance channels, measured in cm.

• Bolus presence time (BPT): time between bolus entrance and exit recorded in the distal channel, measured in seconds.

GER events

A GER event was defined as a retrograde drop in impedance to 50% of baseline of at least 5 s, beginning in the most distal channel and proceeding to one or more proximal channels, followed by an im-

pedance recovery of baseline values. The frequency of GER events was measured (GER events/h), along with the following event characteristics:

• Bolus reflux extent (BRE): the proximal extent reached by the refluxate, shown by the number of channels sequentially involved in the impedance drop, measured in number of channels.

• Bolus clearance time (BCT): time from onset, at the 50% drop in impedance signal from baseline, to the end of the event, at the 50% recovery point from nadir to baseline, recorded in the distal impedance channel, measured in s.

Data analysis

The distribution of all the continuous variables was assessed by the Shapiro-Wilk test. The differences in MII variables between different groups of infants were evaluated with the Mann-Whitney test; the Wilcoxon test was used to compare paired data. Group correlations were analyzed with the Spearman correlation test. Statistical significance was set at $p < 0.05$. Data are presented as median (interquartile range) unless otherwise indicated. Statistical analysis was performed using the STATISTICA software package for Windows (StatSoft, Inc., Tulsa, OK, USA).

Ethics

Written informed consent was obtained from the parents of all included patients. The study was approved by the Ethics Committee of the S.Anna-Regina Margherita Children's Hospital (Protocol no.70823/A2.10-06/20/2013) and was registered at www.clinicaltrials.gov as #NCT02167984.

RESULTS

Sixty-one newborns were eligible for inclusion. Seven of them had MII tracings that were of lower quality due to the presence of artifacts (crying or irritability during MII/pH) or incomplete data, and were excluded from the study. Therefore the final study sample consisted of 54 newborns (23 preterm). At birth, the newborns had a gestational age of 37.0

(33-39) weeks, a body length of 47.1 (43.4-50.0) cm, and a weight of 2,780 (2,043-3,285) g. At MII/pH the newborns had a postmenstrual age of 41.8 (38.7-43.6) weeks, an age of 24 (18-40.5) d, and a body length and weight of 51.5 (49.0-53.5) cm and 3,340 (2,890-3,895) g, respectively.

Over a total of 162 hours of MII/pH, 3,812 ES and 668 GER events were detected. During mealtime 486 ES events (9 consecutive ES events/newborn) were considered in the analysis: BHAT, BHATc, and BPT were 1.31 (1.96-1.89) s, 0.20 (0.15-0.29) s/cm, and 4.71 (3.49-6.27) s, respectively. During the postprandial period 3315 ES events were detected with a frequency of 14.00 (11.17-18.33) events/h. BHAT, BHATc, and BPT were 3.33 (2.68-4.00) s, 0.47 (0.39-0.64) s/cm, and 2.66 (1.83-3.73) s, respectively.
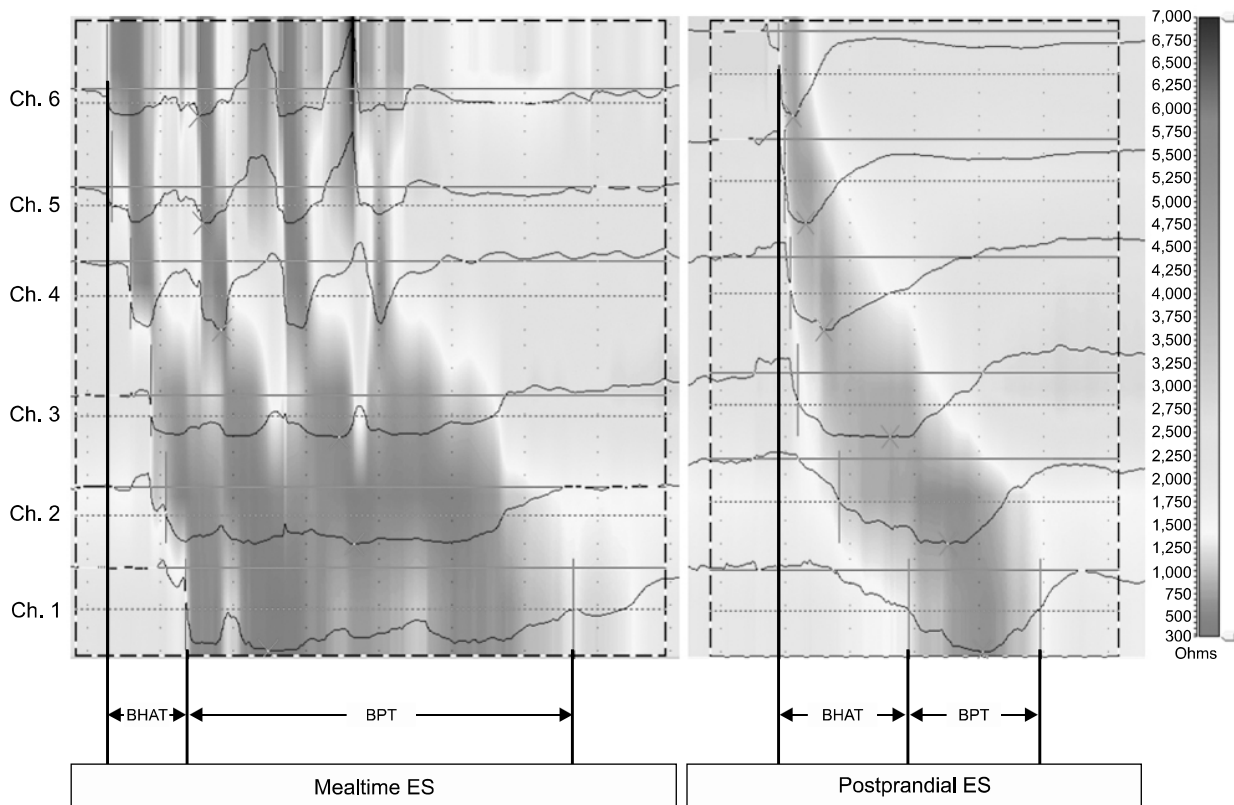
Comparing the characteristics of ES events in mealtime and the postprandial period, BHAT and BHATc were longer ($p < 0.05$) in ES events that occurred during the postprandial period, while BPT was longer ($p < 0.001$) for ES events that occurred during mealtime (Fig. 1).

GER events were detected exclusively during the postprandial period, with a frequency of 4.0 (2.8-5.3) events/h, a BRE of 4.5 (4.2-4.7) cm, and a BCT of 16.7 (12.3-24.1) s.

During mealtime there was no difference in any characteristics of ES events between preterm and term newborns, while during the postprandial period longer BHAT, BHATc and BPT were observed in preterm infants (Table 1). There was no difference in any characteristics of GER events between preterm and term newborns (Table 1).

Analyzing the relationship between the characteristics of ES and GER, we found a significant positive correlation between BHATc and BCT ($\rho = 0.33$,

Fig. 1. Impedance characteristics of esophageal swallow (ES) events during mealtime and the postprandial period. Ch.: impedance channel, BHAT: bolus head advancing time, BPT: bolus presence time.

Table 1. Anthropometric Data and Characteristics of ES and GER Events in 23 Preterm and 31 Term Newborns

	Preterm newborns	Term newborns	p-value*
Anthropometric data at birth			
GA (wk)	33.5 (32.50-35.3)	39.60 (38.80-40.5)	<0.001
Weight (g)	1,970 (1,775-2,110)	3,130 (2,945-3,400)	<0.001
Body length (cm)	42.7 (41.1-44.5)	49.9 (48.0-50.1)	<0.001
Anthropometric data at MII			
PMA	38.7 (36.9-41.6)	42.3 (41.3-44.4)	<0.001
Weight (g)	2,750.0 (2,480.0-3,250.0)	3,600.0 (3,325.0-4,020.0)	<0.001
Body length (cm)	48.4 (47.0-50.8)	53.0 (51.4-54.0)	<0.001
ES event characteristics (mealtime)			
ES	9	9	-
BHAT (s)	1.27 (1.01-1.67)	1.35 (0.91-1.99)	0.637
BHATc (s/cm)	0.20 (0.16-0.28)	0.21 (0.14-0.30)	0.909
BPT (s)	5.50 (4.31-6.69)	4.32 (2.64-6.03)	0.107
ES event characteristics (postprandial)			
Frequency (/h)	14.00 (11.17-19.33)	14.00 (11.50-16.33)	0.840
BHAT (s)	3.68 (2.70-4.09)	3.14 (2.61-3.56)	0.024
BHATc (s/cm)	0.54 (0.45-0.68)	0.44 (0.38-0.58)	0.028
BPT (s)	3.82 (3.22-4.85)	2.14 (1.54-2.66)	<0.001
GER event characteristics (postprandial)			
Frequency (/h)	5.00 (2.83-5.83)	4.00 (2.83-4.67)	0.119
BRE (cm)	4.33 (3.97-4.58)	4.60 (4.41-4.78)	0.052
BCT (s)	19.65 (13.99-27.83)	16.29 (11.87-22.56)	0.189

Values are presented as median (interquartile range) or number only.
ES: esophageal swallow, GER: gastroesophageal reflux, GA: gestational age, MII: multichannel intraluminal impedance, PMA: postmenstrual age, BHAT: bolus head advancing time, BHATc: bolus head advancing time corrected for esophageal length, BPT: bolus presence time, BRE: bolus reflux extent, BCT: bolus clearance time.
*Mann-Whitney test for unpaired data was used to assess statistical significances.

$p < 0.016$) (Fig. 2), whereas there was no significant correlation between BPT and BCT ($\rho = 0.21$, $p < 0.128$). No relationship was found between the characteristics of ES events and the GER event characteristic BRE (BHAT: $\rho = -0.14$, $p < 0.304$; BHATc: $\rho = 0.12$, $p < 0.391$; BPT: $\rho = -0.22$, $p < 0.107$), nor between the frequency of ES and GER events ($\rho = 0.11$, $p < 0.449$).

DISCUSSION

In recent years, the accuracy of MII in evaluating esophageal bolus transit has made its use widespread. In addition to the suitability of MII for the evaluation of GER in infants, the possibility of using it to evaluate esophageal bolus transit during ES events has also been emerging. In adult studies MII is referred to as a sensitive and specific technique for the evaluation of esophageal bolus transit during ES
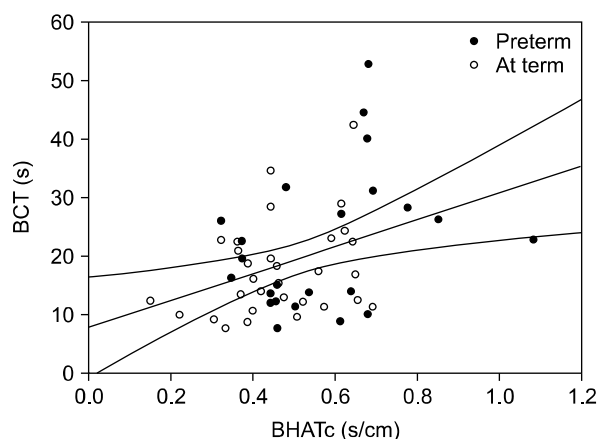
Fig. 2. Spearman correlation for bolus head advancing time corrected for esophageal length (BHATc) and bolus clearance time (BCT).

and GER events [16]. MII has been validated against videofluoroscopy and manometry [12,17], and it has recently been used in combination with esophageal

manometry in adult [18,19] and pediatric studies [11,20-22]. However, to our knowledge the present study is the first to investigate ES and GER events together in a sample of newborns who underwent MII/pH for GERD symptoms.

Our first aim was to evaluate the frequency and characteristics of ES and GER events in these newborns during mealtime and during the postprandial period, in particular BHATc and BPT. BHATc represents the time the bolus head requires to cover the distance between the proximal channel and the distal one (i.e., BHAT), corrected for esophageal length in order to account for the variability of lengths present in a pediatric population. BPT represents the time the bolus takes to pass through the distal channel.

Comparing our data with those obtained from children aged 5-10 years with GERD symptoms [11], we observed a slower average total propagation velocity (1/BHATc) of the bolus in newborns (2.06 cm vs. 2.35 cm) confirming the presence of immature esophageal peristalsis in these patients. Indeed, the organization of esophageal peristalsis seems to start at 27 weeks of gestation and matures as the newborn grows [23,24].

Moreover, our data showed a prolonged BPT and BHATc in preterm compared to term newborns, confirming the previously reported presence of impaired esophageal bolus transit in preterm newborns [25,26].

ES events observed during mealtime were characterized by multiple rapid drops in impedance in the proximal channels, which merged into a single prolonged drop of impedance in the distal channel (Fig. 1). This pattern results from multiple swallows of small boluses that that occur in quick succession and flow together in a single bolus of greater volume distally in the esophagus. This is typical of neonatal sucking and is the reason for the prolonged BPT observed during mealtime, which is an expression of the bolus permanence in the more distal esophageal channel.

BHATc during mealtime was lower than during the postprandial period. We speculate that this lower BHATc could be due to more effective and better organized peristalsis during suction. Indeed, the transport of swallowed milk into the stomach is performed principally by primary peristalsis [27,28], whereas in the postprandial period secondary peristalsis dominates; it arises in the esophagus triggered by the stimulation of esophageal sensory receptors due to the presence of bolus residues not completely eliminated by the primary peristaltic wave, or by GER, with the purpose of clearing these residues [29].

The second aim of the study was to investigate the relationship between the characteristics of ES and GER events. We found a significant positive correlation between BHATc and BCT. Prolonged BCT is an indicator of symptom duration in newborns with GERD [30], and may contribute to the severity of GERD in newborns by increasing esophageal exposure to refluxed material from the stomach. Many factors affect the duration of BCT: volume and viscosity of the refluxed material, delayed gastric emptying, anatomic characteristics, and the tone and stability of the lower esophageal sphincter. Our data showed that patients with higher BHATc are more likely to have prolonged BCT, thus suggesting that the quality of esophageal peristalsis (represented by BHATc) may influence esophageal reflux clearance and plays a key role in determining the duration of BCT.

No correlation between the frequency of ES and GER events was found. This suggests that the frequency of ES does not influence that of GER [2,25] and strengthens the key role of lower esophageal sphincter relaxations in the pathogenesis of GERD.

In conclusion, our study reports the characteristics of ES and GER events in newborns with GERD symptoms and proves that MII is a valid technique to evaluate these events at the same time. The analysis of ES events in parallel with GER events provides new information about esophageal activity. In particular, the analysis of postprandial BHATc could help clinicians to identify newborns with prolonged esophageal clearance time due to impaired esophageal motility.

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